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(54) Title: CLASSIFICATION OF LUNG CARCINOMAS USING GENE EXPRESSION ANALYSIS

(57) Abstract: The invention provides a molecular taxonomy of lung carcinoma, the leading cause of cancer death in the United States and worldwide. Oligonucleotide micro arrays were used to analyze mRNA expression levels corresponding to 12,600 transcript sequences in 186 lung tumor samples, including 139 adenocarcinomas resected from the lung. Hierarchical and probabilistic clustering of expression data defined distinct subclasses of lung adenocarcinoma. Among these were tumors with high relative expression of neuroendocrine genes and of type II pneumocyte genes, respectively. Retrospective analysis revealed a less favorable outcome for the adenocarcinomas with neuroendocrine gene expression. The diagnostic potential of expression profiling is emphasized by its ability to discriminate primary lung adenocarcinomas from metastases of extrapulmonary origin. These results suggest that integration of expression profile data with clinical parameters could aid in diagnosis of lung cancer patients.

CLASSIFICATION OF LUNG CARCINOMAS USING GENE EXPRESSION ANALYSIS

RELATED APPLICATIONS

[0001] This application claims priority to, and the benefit of, Provisional Patent Application USSN 60/325/962 filed on September 28, 2001, the entire disclosure of which is incorporated by reference herein.

GOVERNMENT SUPPORT

[0002] The invention was supported, in whole or in part, by grant U01 CA84995 from the National Cancer Institute. The Government has certain rights in the invention.

FIELD OF THE INVENTION

[0003] In general, the invention relates to a gene expression based classification of lung cancer and a sub-classification of lung adenocarcinoma. This classification serves as a step towards a new molecular taxonomy of lung tumors and demonstrates the power of gene expression profiling in lung cancer diagnosis.

BACKGROUND

[0004] Carcinoma of the lung claims more than 150,000 lives every year in the United States, thus exceeding the combined mortality from breast, prostate and colorectal cancers. Current lung cancer classification is based on clinicopathological features. Lung carcinomas are usually classified as small cell lung carcinomas (SCLC) or non-small cell lung carcinomas (NSCLC). Neuroendocrine features, defined by microscopic morphology and immuno-histochemistry, are hallmarks of the high-grade SCLC and large cell neuroendocrine tumors and of intermediate/low-grade carcinoid tumors. NSCLC is histopathologically and clinically distinct from SCLC, and is further subcategorized as adenocarcinomas, squamous cell carcinomas, and large cell carcinomas, of which adenocarcinomas are the most common.

[0005] The histopathological sub-classification of lung adenocarcinoma is challenging. In one study, independent lung pathologists agreed on lung adenocarcinoma sub-classification in only 41 % of cases. However, a favorable prognosis for bronchioloalveolar carcinoma (BAC), a histological sub-class of lung adenocarcinoma, argues for refining such distinctions. In addition, metastases of non-lung origin can be difficult to distinguish from lung adenocarcinomas.

[0006] Therefore, there is a need in the art for methods and compositions that are useful to distinguish cancer of lung origin from metastases of non-lung origin, and to distinguish different types of lung cancer.

SUMMARY

[0007] The development of microarray methods for large-scale analysis of gene expression makes it possible to search systematically for molecular markers of cancer classification and outcome prediction in a variety of tumor types. Currently, the only effective prognostic indicator for NSCLC in clinical use is surgical-pathological staging. However, according to the invention, the simultaneous analysis of a large number of independent clinical markers offers a powerful adjunct approach in surgical-pathological staging.

[0008] According to the invention, a comprehensive gene expression analysis of human lung tumors identified distinct lung adenocarcinoma sub-classes that were reproducibly generated across different cluster methods. Notably, the C2 adenocarcinoma subclass, defined by neuroendocrine gene expression, is associated with a less favorable outcome, while the C4 group appears to be associated with a more favorable outcome.

[0009] Hierarchical clustering methods offer a powerful approach for class discovery, but are less useful for determining confidence for the classes discovered. In one aspect of the invention, a bootstrap probabilistic clustering is combined with the hierarchical method to measure the strength of sample-sample association, thereby defining cluster membership with greater confidence.

[0010] Although adenocarcinomas with neuroendocrine features have been reported, unique markers that precisely define such tumors have not been described. In another aspect of the invention, putative neuroendocrine markers, for example, kallikrein 11, that discriminate the C2 tumors from all other lung tumors, are identified. In one embodiment, this marker, which is related to the vasodepressor renal kallikrein, is of clinical interest given the observation of orthostatic hypotension in some lung cancer patients.

[0011] In a further aspect of the invention, putative metastases of extra-pulmonary origin with non-lung expression signatures were discovered among presumed lung adenocarcinomas. According to the invention, gene expression analysis can serve as a diagnostic tool to confirm and identify metastases to the lung.

[0012] In one embodiment, the invention provides lung specific marker arrays. In another embodiment, the invention provides lung specific marker information in computer-accessible

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form. In other embodiments, methods and compositions of the invention are useful for drug selection, drug evaluation, patient prognosis, and patient monitoring.

[0013] Diagnostic methods and arrays of the invention can include all of the markers that are characteristic of one or more classes or subclasses of cancer described herein. Alternatively, single markers can be used. Preferably 1 to 20, 1 to 10, or about 5 genetic markers are used in an assay or on an assay to diagnose or detect a specific type of cancer. A single assay may be used to diagnose or detect one or more classes or subclasses of cancer disclosed herein. A useful assay includes one or more markers of one or more classes or subclasses of cancer. Preferred markers for different classes and subclasses of cancer are shown in Tables 1-9.

[0014] Drug screening methods of the invention involve assaying candidate compounds or drugs for their effect on one or more markers of one or more difference classes or subclasses of cancer described herein. Preferably 1 to 20, 1 to 10, or about 5 genetic markers are used in a screening assay to identify a drug that is effective to reduce the expression level of at least one of the markers. Preferred markers for different classes and subclasses of cancer are shown in Tables 1-9. Preferred drug candidates reduce the expression of markers associated with all classes of cancer. However, drug candidates that reduce the expression of markers associated with one or a subset of classes of cancer are also useful. Drug candidates identified in these assays are preferably subject to clinical testing to evaluate their effectiveness against different types of cancer, including different classes and subclasses of lung cancer.

[0015] According to the invention, markers shown to be overexpressed in different types of cancer (including different classes or subclasses of lung cancer) can be used as targets for drug development. Useful drugs include antisense nucleic acids that decrease the expression of one or more markets described herein. Useful drugs also include antibodies or other compounds that interfere with the gene product of one or more markers of the invention. For example, a protease inhibitor that inhibits the activity of kallikrein 11 may be therapeutically useful.

DESCRIPTION OF THE DRAWINGS

[0016] Figure 1. Survival analysis of neuroendocrine C2 adenocarcinomas is shown. Kaplan-Meier curves for C2 versus all other adenocarcinomas. *A*, All patients. C2 (n = 9) and non-C2 (n = 117). B, Patients with stage I tumors only. C2 (n = 4) and non-C2 (n = 72).

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[0017] Figure 2. A computer system is shown. The Memory can be a RAM, ROM, CDROM, Tape, Disk, or other form of memory. The Removable data medium can be a magnetic disk, a CDROM, a tape, an optical disk, or other form of removable data medium.

[0018] Figure 3. A box plot of median array intensity across IVT batches is shown and examples of uncorrected and corrected non-linear responses on same specimens following linear and non-linear scaling methods are also shown.

[0019] Figure 4. Non-linear responses in reference RNA samples are shown following linear scaling (a, c and e) that is corrected after rank invariant scaling (b, d and f).

[0020] Figure 5. Pairwise agreement (R.sq values) of 12600 rank invariant scaled expression values of genes are shown between replicate arrays.

[0021] Figure 6. Clusters selected by AutoClass over several runs of the algorithm are shown. The left panel plots the distribution over 200 runs of the algorithm on the original data set (experiment 1), and on the bootstrapped data sets (experiment 2), both defined over 675 genes. The right panel plots the corresponding distributions with respect to the data sets defined over 1514 genes.

DETAILED DESCRIPTION OF THE INVENTION

[0022] The invention provides methods and compositions for classifying lung carcinomas based on gene expression information. In general, the invention relates to the analysis of gene expression information in normal and cancerous lung tissue and the identification of types or classes of lung cancer based on different patterns of gene expression in different lung carcinomas. In addition, the invention provides specific markers of the different types and classes of lung cancer. According to the invention, markers are useful to classify and evaluate new lung cancers, to provide a prognosis for a lung cancer patient, to identify drugs, and to monitor the progression of a lung cancer in a patient.

[0023] According to the invention, gene expression can be assayed by analyzing and/or quantifying the nucleic acid (including mRNA, rRNA, tRNA and other RNA products of gene transcription) or protein (including short peptide and other protein translation products) products of gene expression. Methods for measuring gene expression are known in the art, and examples are discussed herein. However, one of ordinary skill in the art will understand that methods of the invention relate to all assays of gene expression in normal or diseased lung samples.

[0024] In one embodiment, a gene expression analysis of 186 human carcinomas from the lung provides evidence for biologically distinct sub-classes of lung adenocarcinoma.

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[0025] More fundamental knowledge of the molecular basis and classification of lung carcinomas is useful in the prediction of patient outcome, the informed selection of currently available therapies, and the identification of novel molecular targets for chemotherapy. The recent development of targeted therapy against the Abl tyrosine kinase for chronic myeloid leukemia illustrates the power of such biological knowledge.

Molecular Classification of Diverse Lung Tumors.

[0026] The present invention provides methods for classifying diverse lung tumors based on gene expression profiles. In preferred embodiments, lung tumors are classified based on the expression of a set of marker genes characteristic of a type of lung cancer. In a more preferred embodiment, classification is based on the expression of between 1 and 50, preferably between 1 and 20, more preferably between 1 and 10, and more preferably between 5 and 10 marker genes, the expression of which is strongly correlated with a type of lung cancer.

[0027] First, hierarchical clustering (Eisen, M. B., Spellman, P. T., Brown, P. O. & Botstein, D. (1998) Proc Natl Acad Sci USA **95**, 14863-8) was applied to classify all 203 samples using the 3312 most variably expressed transcripts. The resulting clusters recapitulated the distinctions between established histologic classes of lung tumors-pulmonary carcinoid tumors, SCLC, squamous cell lung carcinomas, and adenocarcinomasthus validating the experimental and analytic approach of the invention. Two-dimensional hierarchical clustering of 203 lung tumors and normal lung samples was performed with 3,312 transcript sequences. The expression index for each transcript was normalized. Adenocarcinomas resected from the lung and a subset of adenocarcinomas suspected as colon metastases were analyzed.

[0028] Normal lung samples form a distinct group, but are most similar to the adenocarcinomas. Marker genes that characterize normal lung samples include TGFβ receptor type II, tetranectin and ficolin 3. A cluster of genes with high relation expression in normal lung includes: TGF-β receptor II; epithelial membrane prot. 2; PECAM-1 (CD31 antigen); PECAM-1 (CD31 antigen); cadherin 5, type 2, VE-cadherin; AF070648; four and a half LIM domains 1; microfibrillar-associated prot. 4; amine oxidase, copper containing 3; A kinase anchor prot. 2; ficolin 3; receptor activity modifying prot. 2; tetranectin; adv. glycosylation end prod.-sp. receptor; TEK tyrosine kinase, endothelial; and slit homolog 2. Elevated TGFβ receptor type II levels have been previously reported for normal bronchial and alveolar epithelium compared to lung carcinomas.

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[0029] SCLC and carcinoid tumors both show high-level expression of neuroendocrine genes including insulinoma-associated gene 1 (Ball, D. W., Azzoli, C. G., Baylin, S. B., Chi, D., Dou, S., DonisKeller, H., Cumaraswamy, A., Borges, M. & Nelkin, B. D. (1993) Proc Natl Acad Sci USA **90**, 5648-52, Lan, M. S., Russell, E. K., Lu, J., Johnson, B. E. & Notkins, A. L. (1993) Cancer Res **53**, 4169-71), achaete scute homolog 1 (Ball, D. W., Azzoli, C. G., Baylin, S. B., Chi, D., Dou, S., DonisKeller, H., Cumaraswamy, A., Borges, M. & Nelkin, B. D. (1993) Proc Natl Acad Sci USA **90**, 5648-52, Lan, M. S., Russell, E. K., Lu, J., Johnson, B. E. & Notkins, A. L. (1993) Cancer Res **53**, 4169-71), gastrin-releasing peptide and chromogranin A. Several previously undescribed markers for SCLC such as thymosin-β and the cell cycle inhibitor $p18^{ink4C}$ were also observed. A cluster of genes with high relative expression in neuroendocrine tumors (small cell lung cancer and pulmonary carcinonas) includes: tubulin, β polypeptide; insulinoma-associated 1; extra spindle poles, yeast homolog; core-binding factor, (runt), α subunit 2; guanine nucleotide binding prot. 4; achaete-scute homolog-like 1; achaete-scute homolog-like 1; CDKN2C (p18); forkhead box G1B; thymosin β, neuroblastoma; ISL1 transcription factor; distal-less homeobon 6; transcription factor 12 (HTF4); PC4 and SFRS1 interacting prot. 2. In one embodiment of the invention, only a few markers are shared between SCLC and carcinoids, while a distinct group of genes defines carcinoid tumors. Two-dimensional hierarchical clustering of 203 lung tumor and normal samples (data set A) was performed with 3,312 genes as described herein. Different clusters of genes with high relative expressions were observed for normal lung; lung carcinoid; small cell lung carcinoma; squamous cell lung carcinoma; and colon metastasis. Clusters C1, C2, C3 and C4 were defined by clustering of data set B. This suggests that carcinoids are highly divergent from malignant lung tumors.

[0030] Squamous cell lung carcinomas, for which diagnostic criteria include evidence of squamous differentiation such as keratin formation form a discrete cluster with high-level expression of transcripts for multiple keratin types and the keratinocytespecific protein stratifin. A cluster of genes with high relative expression in squamous cell lung carcinomas with keratin markers includes: glypican 1; collagen, type VII, α 1; desmoglein 3; W27953; keratin 17; keratin 5; tumor prot. 63; keratin 6; ataxia-telangiectasia group D-assoc. prot.; serine proteinase inhibitor, clade B (5); bullous pemphigoid antigen 1; KIAA0699; CaN19/M87068; S100 calcium-binding prot. A2; and galectin 7. The squamous tumors also show over-expression of p63, a p53-related gene essential for the formation of squamous

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epithelia. Several adenocarcinomas that express high levels of squamous associated genes, also display histological evidence of squamous features.

[0031] Finally, expression of proliferative markers, such as *PCNA*, thymidylate synthase, *MCM2* and *MCM6*, is highest in SCLC, which is known to be the most rapidly dividing lung tumor A cluster of genes with high relative expression associated with proliferation includes: MCM2; MCM6; Rad2; flap structure-specific endonuclease 1; PCNA; thymidylate synthetase; DEK oncogene; H2A histone family, member Z; high-mobility group prot. 2; and ZW10 interactor. However, unlike the other major lung tumor classes shown above, lung adenocarcinomas were not defined by a unique set of marker genes.

Class Discovery among Lung Adenocarcinomas.

[0032] Strong signatures in other lung tumors may obscure the successful subclassification of lung adenocarcinoma in the above analysis. Therefore, a hierarchical clustering was used to sub-classify a data set restricted to adenocarcinomas. Classifications derived by hierarchical clustering and probabilistic clustering algorithms were compared. A two-dimensional colored matrix was generated as a visual representation of a corresponding numerical matrix whose entries record a normalized measure of association strength between samples. Strong association approaches a value of 1 and poor association is close to 0. Associations were obtained for colon metastasis; normal lung; C1 through C4 (adenocarcinoma clusters); additional groups with weaker association were also observed (groups I, II, and III). Genes expressed at high levels in specific subsets of adenocarcinomas can be clustered as a function of histologic differentiation within lung adenoma sub-classes. To avoid spurious variations contributing to the clustering process, 675 transcript sequences were selected with expression levels that were most highly reproducible in duplicate adenocarcinoma samples, yet whose expression varied widely across the chosen sample set (Dataset B); as discussed in the Examples. Normal lung specimens were included in this dataset, as normal epithelium is a component of the grossly dissected adenocarcinoma samples.

[0033] To reduce potential classification-bias due to choice of clustering method, and to clarify adenocarcinoma sub-class boundaries, a model-based probabilistic clustering method (Kang, Y., Prentice, M. A., Mariano, J. M., Davarya, S., Linnoila, R. I., Moody, T. W., Wakefield, L. M. & Jakowlew, S. B. (2000) Exp Lung Res **26**, 685-707) was also used. To assess the overall strength of each pair-wise association, the frequency with which two samples appeared together was measured in a cluster in 200 clustering iterations over bootstrap data sets. A stable cluster was defined as a set of at least 10 samples with a high

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degree of association (a threshold of 0.45 was used, corresponding to shared cluster membership in at least 45% of the bootstrap datasets in which both samples were included). According to this definition, several clusters suggested by the hierarchical tree are stable. These associations can be shown, as a color matrix overlaid on a tree structure obtained from hierarchical clustering. The blocks of associated samples show that both clustering methods recognized subclasses corresponding to normal lung and putative colon metastases (CM). Four subclasses of primary lung adenocarcinoma (C 1 to C4) were also observed by both probabilistic and hierarchical clustering. Several smaller and/or less robust groups were also observed (Groups I, II, and III).

[0034] Probabilistic clustering also revealed correlations between samples that do not directly cluster together. For example, although cluster C4 falls in the right branch of the hierarchical dendrogram with normal lung, it shows significant association with some subclasses in the left dendrogram (groups I and III and cluster C3) but not with other subclasses (clusters CM, C1, and C2).

[0035] Clusters C2, C3, and C4 were also seen as coherent adenocarcinoma groups within the hierarchical clustering of the larger set of lung tumors using the 3,312 transcript sequence set (Dataset A). The reproducible generation of these adenocarcinoma subclasses, across both clustering methods and both gene sets analyzed, supports the validity of the adenocarcinoma clusters and their boundaries.

[0036] In order to identify genes that best defined the proposed clusters, a supervised approach was used to extract marker genes from the entire set of 12,600 transcript sequences. For each cluster, selected genes were the most preferentially expressed in the cluster relative to all other samples, using the signal-to-noise metric described previously (Golub, T. R., Slonim, D. K., Tamayo, P., Huard, C., Gaasenbeek, M., Mesirov, J. P., Coller, H., Loh, M. L., Downing, J. R., Caligiuri, M. A., et al. (1999) Science 286, 5317). The genes whose expression correlated best with each class are useful as markers for class prediction of unknown lung cancer samples.

Identification of Adenocarcinomas Metastatic to the Lung.

[0037] The present invention provides methods for identifying metastatic tumors of non-lung origin. A key issue in lung tumor diagnosis is the discrimination of a primary lung adenocarcinoma from a distant metastasis to the lung. One distinct hierarchical cluster of 12 samples was identified that most likely represent metastatic adenocarcinomas from the colon. These tumors express high levels of galectin-4, *CEACAMI* and liverintestinal cadherin 17, as

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well as c-myc, which is commonly overexpressed in colon carcinoma. Genes expressed at high levels in colon metastases include: c-myc; ETS-2; expressed in thyroid; cadherin 17, (liver-intestine); galectin-4; transmem. 4 superfam. mem. 3; integrin, α 6; trypsin 4, brain; diacylglycerol O-acyltransferase; E74-like factor 3 ; claudin 4; claudin 3; KIAA0792 gene product; CEA CAM-1; and immediate early response 3. Of the 10 samples in this group for which clinical history and/or histopathologic information was available, only 7 samples had been previously diagnosed as metastases of colonic origin. Other adenocarcinomas that showed nonlung signatures included AD 163, which expressed several breast-associated markers including estrogen receptor and mammaglobin, and was associated with a clinical history and histopathology consistent with breast metastasis. Also, AD368, which was not identified as a metastasis, expressed high levels of albumin, transferrin, and other markers associated with the liver. Thus, clustering identified suspected metastases of extra-pulmonary origin, including some that were previously undetected. Accordingly, methods of the invention can play a pivotal role for gene expression analysis in lung tumor diagnosis.

Molecular Signature of Lung Adenocarcinoma Sub-Classes.

[0038] The present invention also provides methods for identifying subclasses of lung adenocarcinoma. Hierarchical and probabilistic clustering defined four distinct sub-classes of primary lung adenocarcinomas. Tumors in the C 1 cluster express high levels of genes associated with cell division and proliferation (ubiquitin carrier prot.; Cks-Hs2; high-mobility group prot. 2; flap structure-specific endonuclease 1; MCM6; thymidine kinase 1; PCNA; and W27939), some of which are also expressed in the squamous cell lung carcinoma and SCLC samples in Dataset A. Relatively high-level expression of proliferation-associated genes was also seen in cluster C2.

[0039] Several neuroendocrine markers, such as dopa decarboxylase and achaete-scute homolog 1, define cluster C2 (kallikrein 11; dopa decarboxylase; achaete-scute homolog-1; achaete-scute homolog-1; calcitonin-related polypeptide α ; proprotein convertase subtilisin; and carboxypeptidase E) and some of these are also expressed in SCLC and pulmonary carcinoids. However, the serine protease, kallikrein 11, is uniquely expressed in the neuroendocrine C2 adenocarcinomas, and not in other neuroendocrine lung tumors.

[0040] C3 tumors are defined by high-level expression of two sets of genes. Expression of one gene cluster (ATPase, Na+/K+ transporting; mesothelin; S100 calcium-binding prot. P; solute carrier family 16; KIAA0828; phospholipase A2, group X; progastricsin (pepsinogen C); cytokine receptor-ike factor 1; dual specificity phosphatase 4; ornithine decarboxylase 1;

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ornithine decarboxylase 1; TS deleted in oral cancer-related 1; ribosomal S6; sodium channel, nonvoltage-gated 1 α; DKFZP564O0823; glutathione S-transferase pi; glutathione S-transferase pi; and hepsin), including ornithine decarboxylase 1 and glutathione S-transferase pi, is shared with the neuroendocrine C2 cluster. Expression of the second set of genes is shared with cluster C4 and with normal lung. Genes expressed at high levels in C4, C3 and normal lung include: surfactant, pulmonary-assoc. prot. B; ~N acylsphingosine amidohydrolase; cytochrome b-5; cytochrome b-5; deleted in liver cancer 1; Ca+ channel, voltage-dependent; surfactant, pulmonary-assoc. prot. C; surfactant, pulmonary-assoc. prot. D; AL049963; ATP-binding cassette (ABC1); KIAA0018 gene product; cathepsin H; selenium binding protein 1; KIAA0758; leukotriene A4 hydrolase; AFO35315; leukocyte protease inhibitor; and BENE. Highest expression of type II alveolar pneumocyte markers, such as thyroid transcription factor 1, and surfactant protein B, C and D genes, was seen in cluster C4, followed by normal lung and C3 cluster. Other markers that defined cluster C4 included cytochrome b5, cathepsin H, and epithelial mucin 1.

Relation between Gene Expression Tumor Classes, Histological Analysis and Smoking History.

[0041] Cluster C1 primarily contains poorly differentiated tumors, while C3 and C4 contains predominantly well-differentiated tumors. Adenocarcinomas of cluster C2 fell in between. Ten of the 14 C4 tumors had been identified as BACs by at least one out of three pathologists who examined the tumors; in contrast, 15 of the remaining 113 adenocarcinomas were similarly described as BACs. The presence of type 11 pneumocyte markers and the high fraction of putative BACs suggest that cluster C4 is likely to be a gene expression counterpart to BAC. All of the C4 tumors in this study were surgical-pathological stage I tumors.

[0042] Although microscopic analysis indicated that samples varied in homogeneity, contamination of normal lung cells does not seem to have overwhelmed the expression signatures. The degree to which tumors clustered with normal samples did not reflect the percentage of tumor cells in a sample in most cases. Class C4 is most similar to normal lung in both hierarchical and probabilistic clustering, yet these tumors all revealed at least an estimated 50% tumor nuclei and in most samples over 80%. In contrast, classes C2 and CM contain tumors with as few as 30% estimated tumor nuclei but are sharply distinguishable from the normal lung. Note that only adenocarcinoma specimen AD363, with an estimated 30% tumor content in the adjacent section, clustered with normal lung.

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[0043] Two adenocarcinoma sub-classes were associated with lower tobacco smoking histories. The presumed metastases of colon origin (CM) and C4 adenocarcinomas with type II pneumocyte gene expression have median smoking histories of 2.5 and 23 pack-years, respectively. The entire data set had a median smoking history of 40 pack-years.

Correlation of Patient Outcome with Putative Adenocarcinoma Classes.

[0044] The present invention also provides methods for predicting patient outcome based on the analysis of lung marker gene expression. Lung cancer patient outcome was correlated with the sub-classes of lung adenocarcinomas defined herein. The neuroendocrine C2 adenocarcinomas were associated with a less favorable survival outcome than all other adenocarcinomas (Fig. 1*A*, 1*B*). The median survival for C2 tumors was 21 months compared to 40.5 months for all non-C2 tumors ($P = 0.00476$). When only stage I tumors are considered, the median survival for patients with C2 tumors was 20 months compared to 47.8 months for patients with non-C2 tumors; as the numbers are smaller, the *P*-value for this comparison is 0.0753. In contrast, C4 adenocarcinomas with type II pneumocyte gene expression (n=14) were associated with a more favorable survival outcome than non-C4 tumors. The median survival for patients with C4 tumors was 49.7 months while the median survival for patients with non-C4 tumors was 33.2 months ($P = 0.049$; note that the non-C2 and non-C4 groups are different because of the exclusion of each group separately in the comparison). For patients with stage I tumors, the median survival in the C4 group was 49.7 months and 43.5 months in the non-C4 group ($P = 0.191$). There was no detectable difference in prognosis between the primary lung adenocarcinomas and the metastases to the lung of colonic origin.

Arrays of gene expression detection agents.

[0045] The present invention also provides arrays of gene expression detection agents. Preferred gene expression detection agents hybridize specifically to marker genes disclosed herein. Such agents may be RNA, DNA, or PNA molecules. Preferred agents are oligonucleotides. Alternative agents bind specifically to the protein expression products of the marker genes disclosed herein. Preferred agents include antibodies and aptamers.

[0046] Agents, such as oligonucleotides, are preferably attached to a solid support in the form of an array. Oligonucleotide arrays in the form of gene chips and useful hybridization assays are known in the art and disclosed for example in U.S. Patent Nos. 5,631,734; 5,874,219; 5,861,242; 5,858,659; 5,856,174; 5,843,655; 5,837,832; 5,834,758; 5,770,722;

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5,770,456; 5,733,729; 5,556,752; 6,045,996; and 6,261,776. In a preferred embodiment, an array includes oligonucleotides for measuring the expression level of markers for a specific type or class of lung cancer. In a more preferred embodiment, an array of the invention includes a plurality of oligonucleotides that are specific for marker for several types or classes of lung cancer or adenocarcinoma.

Information about marker genes and marker gene expression levels.

[0047] The present invention further provides databases of marker genes and information about the marker genes, including the expression levels that are characteristic of different lung cancer types or lung adenocarcinoma subclasses. According to the invention, marker gene information is preferably stored in a memory in a computer system (Fig. 2). Alternatively, the information is stored in a removable data medium such as a magnetic disk, a CDROM, a tape, or an optical disk. In a further embodiment, the input/output of the computer system can be attached to a network and the information about the marker genes can be transmitted across the network.

[0048] Preferred information includes the identity of a predetermined number of marker genes the expression of which correlates with a particular type of lung cancer or a particular subclass of adenocarcinoma. In addition, threshold expression levels of one or more marker genes may be stored in a memory or on a removable data medium. According to the invention, a threshold expression level is a level of expression of the marker gene that is indicative of the presence of a particular type or class of lung cancer.

[0049] In a highly preferred embodiment, a computer system or removable data medium includes the identity and expression information about a plurality of marker genes for several types or classes of lung cancer disclosed herein. In addition, information about marker genes for normal lung tissue may be included.

[0050] Information stored on a computer system or data medium as described above is useful as a reference for comparison with expression data generated in an assay of lung tissue of unknown disease status.

[0051] Finally, the present invention provides methods for identifying, evaluating, and monitoring drug candidates for the treatment of different lung cancer types or adenocarcinoma subclasses. According to the invention, a candidate drug is assayed for its ability to decrease the expression of one or more markers of lung cancer. In one embodiment, a specific drug may reduce the expression of markers for a specific type or subclass of lung carcinoma described herein. Alternatively, a preferred drug may have a

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general effect on lung cancer and decrease the expression of different markers characteristic of different types or classes of lung carcinoma. In one embodiment, a preferred drug decreases the expression of a lung cancer marker by killing lung cancer cells or by interfering with their replication.

[0052] In one embodiment, the screening assays for drug candidates are performed on proteins encoded by the nucleic acids that are identified as having an increased expression in specific subclasses or types of lung carcinoma. In another embodiment, the screening assays for drug candidates are performed on nucleic acids that are differentially expressed in various subclasses or types of lung cancer when compared with normal samples.

[0053] In one embodiment, a candidate drug is added to cells or sample tissue prior to analysis. Preferred cells are cell lines grown from different types of cancer (e.g. different classes or subclasses of lung cancer). Alternatively, cells isolated directly from tumor tissue can be assayed. In another embodiment, the invention provides screens for a candidate drug which modulates lung cancer, modulates lung cancer gene expression and/or protein expression, modulates lung cancer genes or protein activity, binds to a lung cancer protein, or interferes with the binding of a lung cancer protein and an antibody.

[0054] The term "candidate drug" or equivalent as used herein describes any molecule, e.g., an antibody, protein, oligopeptide, fatty acid, steroid, small organic molecule, polysaccharide, polynucleotide, antisense molecule, ligand, bioactive partner and structural analogs or combinations thereof, to be tested for canditate drugs that are capable of directly or indirectly altering the lung cancer phenotype, or the expression of one or more lung cancer markers as identified herein, or overall gene and/or protein expression. Accordingly, methods of the invention include assays for monitoring the expression of nucleic acids and protein.

[0055] Preferred assays screen for candidate drugs that modulate the overall expression of specific gene clusters identified herein (for exampe, one or more genes in Tables 1-9), or the expression of specific nucleic acids or proteins within the clusters. In a particularly preferred embodiment, as assay identified a candidate drug that suppresses a lung cancer phenotype, for example to a normal lung tissue phenotype. A variety of assays can be executed for drug screening. For example, once a specific gene is identified as being differentially expressed by the methods of the invention, candidate drugs that specifically modulate expression or levels of the specific gene may be identified. For example, candidate drugs may be identified that down regulate expression of the specific gene. In one embodiment, candidate drugs may be identified that up regulate expression of the specific gene. Generally a plurality of assay mixtures are run in parallel with different drug concentrations to obtain a differential

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response to the various concentrations. Typically, one of these concentrations serves as a negative control, i.e., at zero concentration or below the level of detection.

[0056] The amount of gene expression can be monitored at either the gene level or the protein level, i.e., the amount of gene expression may be monitored using nucleic acid probes and methods known in the act may be used to qualify gene expression levels. Alternatively, the gene product itself can be monitored, for example through the use of antibodies to the proteins encoded by the nucleic acids identified by the methods of the invention, and in standard immunoassays.

[0057] In one embodiment, candidate drugs or agents are naturally occurring proteins or fragments of naturally occurring proteins. Thus, for example, cellular extracts containing proteins, or random or directed digests of proteinaceous cellular extracts, may be used. In this way libraries of prokaryotic and eukaryotic proteins may be made for *s*creening by the methods of the invention. Particularly preferred in this embodiment are libraries of bacterial, fungal, viral, and mammalian proteins, with the latter being preferred, and human proteins being especially preferred.

[0058] In another embodiment, candidate drugs are peptides of from about 5 to about 30 amino acids, with from about 5 to about 20 amino acids being preferred, and from about 7 to about 15 being particularly preferred. The peptides may be digests of naturally occurring proteins as is outlined above, random peptides, or "biased" random peptides. By "random" or equivalents herein is meant that each nucleic acid and peptide consists of essentially random nucleotides and amino acids, respectively. Since generally these random peptides (or nucleic acids), are chemically synthesized, they may incorporate any nucleotide or amino acid at any position. The synthetic process can be designed to generate randomized proteins or nucleic acids, to allow the formation of all or most of the possible combinations over the length of the sequence, thus forming a library of randomized candidate proteinaceous drugs.

[0059] In another embodiment, the candidate drugs are nucleic acids. As described above generally for proteins, nucleic acid candidate drugs may be naturally occurring nucleic acids or random nucleic acids. For example, digests of prokaryotic or eukaryotic genomes may be used as is outlined above for proteins.

[0060] In a preferred embodiment, nucleic acid drug candidates are antisense molecules. Drug candidates that are antisense molecules include antisense or sense oligonucleotides comprising a single-strand nucleic acid sequence (either RNA or DNA) capable of binding to target mRNA or DNA sequences for lung cancer molecules identified by the methods of the invention. For example, a preferred antisense molecule is a molecule that binds a nucleic

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acid sequence encoding Kallikrein 11. The antisense molecule can either bind a full-length nucleic acid encoding Kallikrein 11, for example the full-length DNA or mRNA encoding Kallikrein 11, or a partial nucleic acid sequence for Kallikrein 11. Antisense or sense oligonuclotides, typically include a fragment of generally about 14 nucleotides, preferably about 14 to 30 nucleotides. However, it is understood that the length of the antisense or sense nucleotides will depend on the length of the target nucleic acid or a fragment thereof.

[0061] In yet another preferred embodiment, drug candidates are antibodies. An antibody used in methods for screening for a candidate drug may either bind a full length protein or a fragment thereof. In a preferred embodiment, the antibody binds a unique epitope on a target protein and shows little or no cross-reactivity. The term "antibody" is understood to include antibody fragments, as are known in the art, including Fab, Fab.sub.2, single chain antibodies (Fv for example), chimeric antibodies, etc., either produced by the modification of whole antibodies or those synthesized de novo using recombinant DNA technologies known in the art.

[0062] Antibodies as used herein as drug candidates include both polyclonal and monoclonal antibodies. Polyclonal antibodies can be raised in a mammal, for example, by one or more injections of an antigenic agent and, if desired, an adjuvant. It may be useful to conjugate the antigenic agent to a protein known to be immunogenic in the mammal being immunized. Preferred antigenic agents include cancer specific antigens, and more preferably lung cancer specific antigens. Examples of adjuvants which may be employed include Freund's complete adjuvant and MPL-TDM adjuvant (monophosphoryl Lipid A, synthetic trehalose dicorynomycolate).

[0063] The antibodies may, alternatively, be monoclonal antibodies. Monoclonal antibodies may be prepared using various hybridoma methods known in the art. For example, a mouse, hamster, or other appropriate host animal, is typically immunized with an immunizing agent to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to a immunizing agent. Alternatively, the lymphocytes may be immunized in vitro. An immunizing agent is preferably a protein or fragment thereof that differentially expressed in subclasses or types of lung cancer. However, other known cancer specific antigens may also be used. In a preferred embodiment, the immunizing agent is the full length Kallikrein 11 protein or a homolog or derivative thereof. In another embodiment, the immunizing agent is a partial-length Kallikrein 11 protein or a homolog or derivative thereof.

[0064] Panels of available antibodies may also be screened for their effect on the expression of lung specific gene clusters (or specific genes or subsets of genes within these clusters). In

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one embodiment, some or all o fthe antibodies being screened are not known to be associated with any cancer specific antigen. In one embodiment, the antibodies are bispecific antibodies. Bispecific antibodies are monoclonal, preferably human or humanized, antibodies that have binding specificities for at least two different antigens.

[0065]

[0066] In yet another embodiment, the candidate drugs are chemical compounds. In a preferred embodiment, the candidate drugs are small organic compounds having a molecular weight of more than 100 and less than about 2500 daltons. Candidate drugs may also include functional groups necessary for structural interaction with proteins or nucleic acids.

[0067] According to the invention, levels of marker genes disclsosed herein can be used the follow the course of a lung cancer in a patient.. Methods of the invention are therefore useful to evalutate the effectiveness of a particular treatment. In addition, methods of the invention are also useful to monitor the progression of a lung cancer in a patient, for example from a C4 to a C3 to a C2 adenocarcinoma.

[0068] The identification of candidates that, alone or admixed with other suitable molecules, are competent to treat lung cancer are contemplated by the invention. Further, the production of commercially significant quantities of the aforementioned identified candidates, which are suitable for the prevention and/or treatment of lung, colon, or other cancer is contemplated. Moreover, the invention provides for the production of therapeutic grade commercially significant quantities of therapeutic agents in which any undesirable properties of the initially identified analog, such as *in vivo* toxicity or a tendency to degrade upon storage, are mitigated.

[0069] Methods of preventing and treating cancer, after the identification of an antibody, peptide, peptidomimetic, nucleic acid, or small molecule, include the step of administering a composition including such a compound to a patient.

[0070] Nucleic acid molecules (including DNA, RNA, and nucleic acid analogs such as PNA) which are themselves active or which code for active expressed products; peptides; proteins; antibodies; or other chemical compounds isolated and identified, or based upon or derived from ligands isolated and identified according to the invention (also referred to as active compounds or drugs) can be incorporated into pharmaceutical compositions suitable for administration. Such active compounds or drugs include inhibitors identified or constructed as a result of isolating and identifying ligands according to the invention. The drug compounds discovered according to the present invention can be administered to a mammalian host by any route. Thus, as appropriate, administration can be oral or parenteral,

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including intravenous and intraperitoneal routes of administration. In addition, administration can be by periodic injections of a bolus of the drug, or can be made more continuous by intravenous or intraperitoneal administration from a reservoir which is external (e.g., an i.v. bag). In certain embodiments, the drugs of the instant invention can be therapeutic-grade. That is, certain embodiments comply with standards of purity and quality control required for administration to humans. Veterinary applications are also within the intended meaning as used herein.

[0071] The formulations, both for veterinary and for human medical use, of the drugs according to the present invention typically include such drugs in association with a pharmaceutically acceptable carrier therefor and optionally other therapeutic ingredient(s). The carrier(s) can be "acceptable" in the sense of being compatible with the other ingredients of the formulations and not deleterious to the recipient thereof. Pharmaceutically acceptable carriers, in this regard, are intended to include any and all solvents, dispersion media, coatings, antibacterial and antifingal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds (identified according to the invention and/or known in the art) also can be incorporated into the compositions. The formulations can conveniently be presented in dosage unit form and can be prepared by any of the methods well known in the art of pharmacy/microbiology. In general, some formulations are prepared by bringing the drug into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation.

[0072] A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include oral or parenteral, e.g., intravenous, intradermal, inhalation, transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide.

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[0073] Useful solutions for oral or parenteral administration can be prepared by any of the methods well known in the pharmaceutical art, described, for example, in Remington's Pharmaceutical Sciences, (Gennaro, A., ed.), Mack Pub., 1990. Formulations for parenteral administration also can include glycocholate for buccal administration, methoxysalicylate for rectal administration, or cutric acid for vaginal administration. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. Suppositories for rectal administration also can be prepared by mixing the drug with a non-irritating excipient such as cocoa butter, other glycerides, or other compositions that are solid at room temperature and liquid at body temperatures. Formulations also can include, for example, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, hydrogenated naphthalenes, and the like. Formulations for direct administration can include glycerol and other compositions of high viscosity. Other potentially useful parenteral carriers for these drugs include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, and liposomes. Formulations for inhalation administration can contain as excipients, for example, lactose, or can be aqueous solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or oily solutions for administration in the form of nasal drops, or as a gel to be applied intranasally. Retention enemas also can be used for rectal delivery.

[0074] Formulations of the present invention suitable for oral administration can be in the form of discrete units such as capsules, gelatin capsules, sachets, tablets, troches, or lozenges, each containing a predetermined amount of the drug; in the form of a powder or granules; in the form of a solution or a suspension in an aqueous liquid or non-aqueous liquid; or in the form of an oil-in-water emulsion or a water-in-oil emulsion. The drug can also be administered in the form of a bolus, electuary or paste. A tablet can be made by compressing or moulding the drug optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing, in a suitable machine, the drug in a free-flowing form such as a powder or granules, optionally mixed by a binder, lubricant, inert diluent, surface active or dispersing agent. Moulded tablets can be made by moulding, in a suitable machine, a mixture of the powdered drug and suitable carrier moistened with an inert liquid diluent.

[0075] Oral compositions generally include an inert diluent or an edible carrier. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients. Oral compositions prepared using a fluid carrier for use as a mouthwash include the compound in the fluid carrier and are applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be

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included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose; a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[0076] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor ELTM (BASF, Parsippany, NJ) or phosphate buffered saline (PBS). In all cases, the composition can be sterile and can be fluid to the extent that easy syringability exists. It can be stable under the conditions of manufacture and storage and can be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyetheylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, and sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[0077] Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation include vacuum drying and freeze-drying which yields a powder of the active

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ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0078] Formulations suitable for intra-articular administration can be in the form of a sterile aqueous preparation of the drug which can be in microcrystalline form, for example, in the form of an aqueous microcrystalline suspension. Liposomal formulations or biodegradable polymer systems can also be used to present the drug for both intra-articular and ophthalmic administration.

[0079] Formulations suitable for topical administration include liquid or semi-liquid preparations such as liniments, lotions, gels, applicants, oil-in-water or water-in-oil emulsions such as creams, ointments or pasts; or solutions or suspensions such as drops. Formulations for topical administration to the skin surface can be prepared by dispersing the drug with a dermatologically acceptable carrier such as a lotion, cream, ointment or soap. In some embodiments, useful are carriers capable of forming a film or layer over the skin to localize application and inhibit removal. Where adhesion to a tissue surface is desired the composition can include the drug dispersed in a fibrinogen-thrombin composition or other bioadhesive. The drug then can be painted, sprayed or otherwise applied to the desired tissue surface. For topical administration to internal tissue surfaces, the agent can be dispersed in a liquid tissue adhesive or other substance known to enhance adsorption to a tissue surface. For example, hydroxypropylcellulose or fibrinogen/thrombin solutions can be used to advantage. Alternatively, tissue-coating solutions, such as pectin-containing formulations can be used.

[0080] For inhalation treatments, inhalation of powder (self-propelling or spray formulations) dispensed with a spray can, a nebulizer, or an atomizer can be used. Such formulations can be in the form of a finely comminuted powder for pulmonary administration from a powder inhalation device or self-propelling powder-dispensing formulations. In the case of self-propelling solution and spray formulations, the effect can be achieved either by choice of a valve having the desired spray characteristics (i.e., being capable of producing a spray having the desired particle size) or by incorporating the active ingredient as a suspended powder in controlled particle size. For administration by inhalation, the compounds also can be delivered in the form of an aerosol spray from a pressured container or dispenser which contains a suitable propellant, e.g., a gas such as carbon dioxide, or a nebulizer. Nasal drops also can be used.

[0081] Systemic administration also can be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be

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permeated are used in the formulation. Such penetrants generally are known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and filsidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds typically are formulated into ointments, salves, gels, or creams as generally known in the art.

[0082] In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials also can be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811. Microsomes and microparticles also can be used.

[0083] Oral or parenteral compositions can be formulated in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

[0084] Generally, the drugs identified according to the invention can be formulated for parenteral or oral administration to humans or other mammals, for example, in therapeutically effective amounts, e.g., amounts which provide appropriate concentrations of the drug to target tissue for a time sufficient to induce the desired effect. Additionally, the drugs of the present invention can be administered alone or in combination with other molecules known to have a beneficial effect on the particular disease or indication of interest. By way of example only, useful cofactors include symptom-alleviating cofactors, including antiseptics, antibiotics, antiviral and antifungal agents and analgesics and anesthetics.

[0085] Where a peptide, peptidomimetic, small molecule or other drug identified according to the invention is to be used as part of a transplant procedure (e.g. a lung transplant

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procedure), it can be provided to the living tissue or organ to be transplanted prior to removal of tissue or organ from the donor. The drug can be provided to the donor host.

[0086] Alternatively, or in addition, once removed from the donor, the organ or living tissue can be placed in a preservation solution containing the drug. In all cases, the drug can be administered directly to the desired tissue, as by injection to the tissue, or it can be provided systemically, either by oral or parenteral administration, using any of the methods and formulations described herein and/or known in the art.

[0087] Where the drug comprises part of a tissue or organ preservation solution, any commercially available preservation solution can be used to advantage. For example, useful solutions known in the art include Collins solution, Wisconsin solution, Belzer solution, Eurocollins solution and lactated Ringer's solution. Generally, an organ preservation solution usually possesses one or more of the following properties: (a) an osmotic pressure substantially equal to that of the inside of a mammalian cell (solutions typically are hyperosmolar and have K+ and/or Mg++ ions present in an amount sufficient to produce an osmotic pressure slightly higher than the inside of a mammalian cell); (b) the solution typically is capable of maintaining substantially normal ATP levels in the cells; and (c) the solution usually allows optimum maintenance of glucose metabolism in the cells. Organ preservation solutions also can contain anticoagulants, energy sources such as glucose, fructose and other sugars, metabolites, heavy metal chelators, glycerol and other materials of high viscosity to enhance survival at low temperatures, free oxygen radical inhibiting and/or scavenging agents and a pH indicator. A detailed description of preservation solutions and useful components can be found, for example, in U.S. Pat. No. 5,002,965, the disclosure of which is incorporated herein by reference.

[0088] The effective concentration of the drugs identified according to the invention that is to be delivered in a therapeutic composition will vary depending upon a number of factors, including the final desired dosage of the drug to be administered and the route of administration. The preferred dosage to be administered also is likely to depend on such variables as the type and extent of disease or indication to be treated, the overall health status of the particular patient, the relative biological efficacy of the drug delivered, the formulation of the drug, the presence and types of excipients in the formulation, and the route of administration. In some embodiments, the drugs of this invention can be provided to an individual using typical dose units deduced from the earlier-described mammalian studies using non-human primates and rodents. As described above, a dosage unit refers to a unitary, i.e. a single dose which is capable of being administered to a patient, and which can be

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readily handled and packed, remaining as a physically and biologically stable unit dose comprising either the drug as such or a mixture of it with solid or liquid pharmaceutical diluents or carriers.

[0089] In certain embodiments, organisms are engineered to produce drugs identified according to the invention. These organisms can release the drug for harvesting or can be introduced directly to a patient. In another series of embodiments, cells can be utilized to serve as a carrier of the drugs identified according to the invention.

[0090] The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

[0091] Drugs identified by a method of the invention also include the prodrug derivatives of the compounds. The term prodrug refers to a pharmacologically inactive (or partially inactive) derivative of a parent drug molecule that requires biotransformation, either spontaneous or enzymatic, within the organism to release the active drug. Prodrugs are variations or derivatives of the compounds of the invention which have groups cleavable under metabolic conditions. Prodrugs become the compounds of the invention which are pharmaceutically active *in vivo*, when they undergo solvolysis under physiological conditions or undergo enzymatic degradation. Prodrug compounds of this invention can be called single, double, triple, and so on, depending on the number of biotransformation steps required to release the active drug within the organism, and indicating the number of functionalities present in a precursor-type form. Prodrug forms often offer advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (see, Bundgard, Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985 and Silverman, The Organic Chemistry of Drug Design and Drug Action, pp. 352-401, Academic Press, San Diego, Calif., 1992). Prodrugs commonly known in the art include acid derivatives known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acids with a suitable alcohol, or amides prepared by reaction of the parent acid compound with an amine, or basic groups reacted to form an acylated base derivative. Moreover, the prodrug derivatives of drugs discovered according to this invention can be combined with other features herein taught to enhance bioavailability.

[0092] Drugs as identified by the methods described herein can be administered to individuals to treat (prophylactically or therapeutically) various stages or subclasses of cancer. In conjunction with such treatment, pharmacogenomics (i.e., the study of the relationship between an individual's genotype and that individual's response to a foreign compound or drug) can be considered. Differences in metabolism of therapeutics can lead to

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severe toxicity or therapeutic failure by altering the relation between dose and blood concentration of the pharmacologically active drug. Thus, a physician or clinician can consider applying knowledge obtained in relevant pharmacogenomics studies in determining whether to administer a drug as well as tailoring the dosage and/or therapeutic regimen of treatment with the drug.

[0093] Pharmacogenomics deals with clinically significant hereditary variations in the response to drugs due to altered drug disposition and abnormal action in affected persons. See e.g., Eichelbaum, M., Clin Exp Pharmacol Physiol, 1996, 23(10-11) :983-985 and Linder, M. W., Clin Chem, 1997, 43(2):254-266. In general, two types of pharmacogenetic conditions can be differentiated. Genetic conditions transmitted as a single factor altering the way drugs act on the body (altered drug action) or genetic conditions transmitted as single factors altering the way the body acts on drugs (altered drug metabolism). These pharmacogenetic conditions can occur either as rare genetic defects or as naturally-occurring polymorphisms. For example, glucose-6-phosphate dehydrogenase deficiency (G6PD) is a common inherited enzymopathy in which the main clinical complication is haemolysis after ingestion of oxidant drugs (anti-malarials, sulfonamides, analgesics, nitroflirans) and consumption of fava beans.

[0094] One pharmacogenomics approach to identifying genes that predict drug response, known as "a genome-wide association," utilizes a high-resolution map of the human genome consisting of already known gene-related markers (e.g., a "bi-allelic" gene marker map which consists of 60,000-100,000 polymorphic or variable sites on the human genome, each of which has two variants). Such a high-resolution genetic map can be compared to a map of the genome of each of a statistically significant number of patients taking part in a Phase II/III drug trial to identify markers associated with a particular observed drug response or side effect. Alternatively, such a high resolution map can be generated from a combination of some ten-million known single nucleotide polymorphisms (SNPs) in the human genome. A SNP is a common alteration that occurs in a single nucleotide base in a stretch of DNA. For example, a SNP can occur once per every 1000 bases of DNA. A SNP can be involved in a disease process, however, the vast majority can not be disease-associated. Given a genetic map based on the occurrence of such SNPs, individuals can be grouped into genetic categories depending on a particular pattern of SNPs in their individual genome. In such a manner, treatment regimens can be tailored to groups of genetically similar individuals, taking into account traits that can be common among such genetically similar individuals.

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[0095] Alternatively, a method termed the "candidate gene approach," can be utilized to identify genes that predict drug response. According to this method, if a gene that encodes a drug's target is known, all common variants of that gene can be fairly easily identified in the population and it can be determined if having one version of the gene versus another is associated with a particular drug response.

[0096] As an illustrative embodiment, the activity of drug metabolizing enzymes is a major determinant of both the intensity and duration of drug action. The discovery of genetic polymorphisms of drug metabolizing enzymes (e.g., N-acetyltransferase 2 (NAT 2) and cytochrome P450 enzymes CYP2D6 and CYP2C19) has provided an explanation as to why some patients do not obtain the expected drug effects or show exaggerated drug response and serious toxicity after taking the standard and safe dose of a drug. These polymorphisms are expressed in two phenotypes in the population, the extensive metabolizer (EM) and poor metabolizer (PM). The prevalence of PM is different among different populations. For example, the gene coding for CYP2D6 is highly polymorphic and several mutations have been identified in PM, which all lead to the absence of functional CYP2D6. Poor metabolizers of CYP2D6 and CYP2CI9 quite frequently experience exaggerated drug response and side effects when they receive standard doses. If a metabolite is the active therapeutic moiety, PM show no therapeutic response, as demonstrated for the analgesic effect of codeine mediated by its CYP2D6-formed metabolite morphine. The other extreme are the so called ultra-rapid metabolizers who do not respond to standard doses. Recently, the molecular basis of ultra-rapid metabolism has been identified to be due to CYP2D6 gene amplification. Alternatively, a method termed the "gene expression profiling," can be utilized to identify genes that predict drug response. For example, the gene expression of an animal dosed with a drug can give an indication whether gene pathways related to toxicity have been turned on.

[0097] Information generated from more than one of the above pharmacogenomics approaches can be used to determine appropriate dosage and treatment regimens for prophylactic or therapeutic treatment an individual. This knowledge, when applied to dosing or drug selection, can avoid adverse reactions or therapeutic failure and thus enhance therapeutic or prophylactic efficiency when treating a subject with a drug identified according to the invention.

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EXAMPLES

Example 1: Materials and Methods

Specimens and Datasets.

[0098] A total of 203 snap-frozen lung tumors (n=186) and normal lung (n=17) specimens were used to create two datasets. Of these, 125 adenocarcinoma samples were associated with clinical data and with histological slides from adjacent sections.

[0099] The 203 specimens (Dataset A) include histologically-defined lung adenocarcinomas (n=127), squamous cell lung carcinomas (n=21), pulmonary carcinoids (n=20), SCLC (n=6) cases and normal lung (n=17) specimens. Other adenocarcinomas (n=12) were suspected to be extrapulmonary metastases based on clinical history. Dataset B, a subset of Dataset A, includes only adenocarcinomas and normal lung samples.

Tumor Bank, Clinical Information, and Pathological Analysis

[00100] The complete cohort for these studies consists of 203 patient samples that can be broken down into 139 lung adenocarcinomas (AD) that included 12 suspected metastases of extrapulmonary origin, 21 squamous (SQ) cell carcinoma cases, 20 pulmonary carcinoid (COID) tumors and 6 small cell lung cancers (SCLC), as well as 17 normal lung (NL) samples.

[00101] Tumor and normal lung specimens in this study were obtained from two independent tumor banks. The following specimens were obtained from the Thoracic Oncology Tumor Bank at the Brigham and Women's Hospital / Dana Farber Cancer Institute: 127 adenocarcinomas, 8 squamous cell carcinomas, 4 small cell carcinomas, and 14 pulmonary carcinoid samples. In addition 12 adenocarcinoma samples without associated clinical data were obtained from the Brigham/Dana-Farber tumor bank. In addition, 13 squamous cell carcinoma, 2 small cell lung carcinoma, and 6 carcinoid samples were obtained from the Massachusetts General Hospital (MGH) Tumor Bank. The snap-frozen, anonymized samples from MGH were not associated with histological sections or clinical data.

[00102] Frozen samples of resected lung tumors and parallel "normal" (grossly uninvolved) lung (protocol 91-03831) for anonymous distribution to IRB-approved research projects were obtained within 30 minutes of resection and subdivided into samples (~100 mg). Samples intended for nucleic acid extraction was snap frozen on powdered dry ice and

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individually stored at –140 °C. Each was associated with an immediately adjacent sample embedded for histology in Optimal Cutting Temperature (OCT) medium and stored at –80 °C. Six micron frozen sections of embedded samples stained with H&E was used to confirm the post operative-pathologic diagnosis and to estimate the cellular composition of adjacent extraction samples as discussed below. Each selected sample was further characterized by examining viable tumor cells in H&E stained frozen sections comprising of at least 30% nucleated cells and low levels of tumor necrosis (<40%). In addition, at least once pulmonary pathologists (I and II) independently evaluated adjacent OCT blocks for tumor type and content. Notes were also taken for extent of fibrosis and inflammatory infiltrates.

[00103] Duplicate blocks, coupled with the identical OCT-embedded block, were also available for 36 of the adenocarcinoma samples. The majority of these duplicate blocks were within 1 to 1.5 cm from one another.

[00104] Clinical data from a prospective database and from the hospital records included the age and sex of the patient, smoking history, type of resection, post-operative pathological staging, post-operative histopathological diagnosis, patient survival information, time of last follow-up interval or time of death from the date of resection, disease status at last follow-up or death (when known), and site of disease recurrence (when known). Code numbers were assigned to samples and correlated clinical data. The linkup between the code numbers and all patient identifiers was destroyed, rendering the samples and clinical data completely anonymous.

[00105] 125 adenocarcinoma samples were associated with clinical data. Adenocarcinoma patients included 53 males and 72 females. There were 17 reported non-smokers, 51 patients reporting less than a 40 pack-year smoking history, and 54 patients reported a greater than 40 pack-year smoking history. The post-operative surgical-pathological staging of these samples included 76 stage I tumors, 24 stage II tumors, 10 stage III tumors, and 12 patients with putative metastatic tumors. Note that numbers do not always add to 125, as complete information could not be found for each case.

RNA extraction and Microarray Experiments

[00106] Briefly, tissue samples were homogenized in Trizol (Life Technologies, Gaithersburg, MD) and RNA was extracted and purified using the RNEASY column purification kit (QIAGEN, Chatsworth, CA). RNA extracted from samples that were collected from two different OCT blocks was given the sample code name followed by the corresponding OCT block name. Denaturing formaldehyde gel electrophoresis followed by

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northern blotting using a beta-actin probe assessed RNA integrity. Samples were excluded if beta-actin was not full-length.

[00107] Preparation of *in vitro* transcription (IVT) products and oligonucleotide array hybridization and scanning were performed according to Affymetrix protocol (Santa Clara, CA). In brief, the amount of starting total RNA for each IVT reaction varied between 15 and 20 mg. First strand cDNA synthesis was generated using a T7-linked oligo-dT primer, followed by second strand synthesis. IVT reactions were performed in batches to generate cRNA targets containing biotinylated UTP and CTP, which was subsequently chemically fragmented at 95 °C for 35 minutes. Ten micrograms of the fragmented, biotinylated cRNA was mixed with MES buffer (2-[N-Morpholino]ethansulfonic acid) containing 0.5 mg/ml acetylated bovine serum albumin (Sigma, St. Louis, MO) and hybridized to Affymetrix (Santa Clara, CA) HGU95A v2 arrays at 45 °C for 16 hours. HGU95A v2 arrays contain ~12600 genes and expressed sequence tags. Arrays were washed and stained with streptavidin-phycoerythrin (SAPE, Molecular Probes). Signal amplification was performed using a biotinylated anti-streptavidin antibody (Vector Laboratories, Burlingame, CA) at 3 μg/ml. A second staining with SAPE followed this. Normal goat IgG (2 mg/ml) was used as a blocking agent. Scans on arrays were performed on Affymetrix scanners and the expression value for each gene was calculated using Affymetrix GENECHIP software. Minor differences in microarray intensity were corrected using a scaling method as detailed below.

Example 2: Data Analysis

Feature Selection and Hierarchical Clustering.

[00108] For Dataset A, a standard deviation threshold of 50 expression units was used to select the 3,312 most variable transcript sequences. For Dataset B, 52 pairs of replicates (representing 36 duplicate adenocarcinomas) were used to determine the quality of the dataset, and 45 pairs having a R^2 value > 0.9 were used to select 675 transcript sequences (features) whose expression varied the most across all sample pairs (Figs. 3-5).

Preprocessing and Re-scaling

[00109] The raw expression data for the first 12600 genes obtained from Affymetrix GENECHIP software was re-scaled to account for different chip intensities. Each column (sample) in the dataset was multiplied by *1/slope* of a least squares linear fit of the sample vs. the reference (a sample in the dataset). The linear fit was done using only genes that have

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'Present' calls in both the sample being re-scaled and the reference. The sample chosen as reference was a typical one (i.e. one with the number of "P" calls closer to the average over all samples in the dataset). The reference sample for the dataset was AD114T1. Scans were rejected if the scaling factor exceeded a factor of 4, fewer than 30% 'Present' calls, or microarray artifacts were visible. Scans that failed the above criterion were re-hybridized and re-scanned on new chips from the same fragmented cDNA.

[00110] However, linear scaling was insufficient to correct for non-linear responses that were observed, which may have resulted from saturation effects or IVT-variations from one batch to the other. Thus, a non-linear scaling was applied to adjust for such differences (Fig. 3). The 2% trimmed mean of "P" genes for all arrays after linear and non-linear rank invariant scaling (described below) are shown in box plots stratified by IVT batches. The batch differences in mean intensity may be due to the fact that a more homogenous IVT processing was applied to arrays in the same IVT batch than arrays in different batches. Also noticeable was the non-linear relationships between the scatter-plots of replicate arrays (Fig. 3) and reference RNA samples (Fig. 4), which justifies non-linear scaling methods to make expression values of genes across arrays more reasonable estimates of the actual expression values for transcripts and overall brightness of arrays.

[00111] A rank-invariant scaling method (Tseng, G. C., Oh, M. K., Rohlin, L., Liao, J. C. & Wong, W. H. (2001) *Nucleic Acids Res* **29,** 2549-57) was used to scale all arrays towards a baseline array (AD114T1). A set of genes whose ranks in the two arrays was smaller than 50 (an empirical value chosen to make the points for selected genes naturally form a tight curve, was used to fit a smoothing spline (Venables, W. N. & Ripley, B. D. (1998) *Modern applied statistics with S-PLUS* (Springer, Berlin)) in the scatter-plot of the array to be normalized (X-axis) and the baseline array (Y-axis). This "Invariant Set" presumably consists of non-differentially expressed genes. The normalized values were determined by reading off the values determined by the smoothing curve for values on X-axis. After scaling the replicate arrays agree better, and batch differences were less dramatic (Fig. 3). Hence, the rank invariant-scaled data was used for all downstream analysis.

Reproducibility Statistics

[00112] Reproducibility controls included independent frozen tissue blocks for 36 adenocarcinomas resected from the lung, 16 replicates of IVT reactions or scans, and 13 reference RNA samples (Stratagene, La Jolla, California). Scaled expression values for 45 of

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the 52 replicates compared were correlated with $R^2 > 0.9$, and for 50 of the 52 replicates with $R^2 > 0.85$. Examples of pairwise correlations between replicates are shown in Fig. 5.

Replication Filtering

[00113] According to the invention, technical noise may affect the measurement of some genes more than others, and the already difficult problem of adenocarcinoma sub-classification might be particularly sensitive to such noise. Accordingly, adenocarcinoma replicates were used to select only highly reproducible features (representing genes) for subsequent use in adenocarcinoma clustering. The reproducibility of 52 pairs of replicate arrays randomly selected across the adenocarcinoma samples was assessed. For each pair of replicates, a single measure of correlation (R^2) was computed across all 12600 genes (Fig. 5). Forty-five replicate pairs with R^2 values greater than 0.9 were used for filtering genes (below).

[00114] For each gene, a scatter plot was generated with the selected 45 pairs of replicate data points. The reproducibility of expression was assessed (Pearson correlation) between replicate pairs as well as the variability of expression values across the 45 pairs. The distribution of 45 pairwise expression datapoints was plotted for genes that were randomly selected. The correlation index of expression (a measure of a gene's variability between samples). To avoid spurious correlation measures 2-4 outliers in each dimension were removed from the calculation of correlation was obtained (cluster Incl W26626:, cor=0.0221; desmoglein 3 (pemphi, cor=0.354; phosphoglucomutase 5, cor=0.311; ATP synthase, H+ tra, cor=0.137;Cluster Incl A14316, cor=0.188; Cluster Incl Y12851, cor=0.2631, solute carrier famil, cor=0.429; zinc finger protein, cor=0.179; Cluster Incl AA5866, cor=0.374; Cluster Incl AA5866, cor=0.315; Cluster Incl M34428, cor=0.351; ets variant gene 2, cor=0.187; RecQ protein-like 5, cor=0.366; Cluster Incl AJ0100, cor=0.378; one cut domain, fami, cor=0.396; hexose-6-phosphate d, cor=0.0165; Cluster Incl AL0223, cor=0.376; synovial sarcoma, X, cor=0.371; Cluster Incl S79325, cor=0.502; Cluster Incl Z84717: and cor=0.513). In addition, genes whose expression levels did not vary significantly across the 45 samples were eliminated because they were unlikely to be informative. The number of features (genes) selected by this filter varied depending on the Pearson correlation cut-off used. A clustering of adenocarcinomas was performed using 675 genes selected by a Pearson correlation threshold of 0.8. These genes have consistent expression values between replicate arrays, and their expression across all adenocarcinoma samples was variable. Selection of genes at Pearson correlation coefficients of 0.7 (1514 genes), 0.75 (1105 genes), or 0.85 (366

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genes) led to roughly similar clustering. The distribution of 45 pairwise expression datapoints was plotted for selected genes that varied between the 45 adenocarcinoma replicates. The spread of the datapoints results in a correlation index that can be used to select genes that are variant between adenocarcinomas. Gene sets were selected based on their correlation cutoffs (0.7, 0.75, 0.8 and 0.85). To avoid spurious correlation measure 2-4 outliers in each dimension were removed from the calculation of correlation. The expression ranges of genes in samples that pass a replicate correlation greater than 0.85 include glyceraldehyde-3-pho, cor=0.873; glycetaldehyde-3-pho, cor=0.861; trefoil factor 3, cor=0.966; thymosin, beta 10, cor=0.862; ribosomal protein L8, cor=0.867; immunoglobulin kappa, cor=0.854; ribosomal protein S1, cor=0.882; melanoma antigen, fa, cor=0.85; epithelial protein u, cor=0.889; metallothionein 1F (,cor=0.88; surfactant, pulmonar, cor=0.921; UDP glycosyltransfer, cor=0.931; melanoma antigen, fa, cor=0.938; phospholipase A2, gr, cor=0.888; proline oxidase homo, cor=0.871 ; melanoma antigen, fa, cor=0.922; ring finger protein, cor 0.91; Cluster Incl AF0151, cor 855; tubulin, alpha, ubiq, cor=0.851, and secretory leukocyte, cor=0.934.

Hierarchical Clustering

[00115] Hierarchical clustering is an unsupervised learning method useful for dividing data into natural groups. Data are clustered hierarchically by organizing the data into a tree structure based upon the degree of correlation between features. CLUSTER (Eisen, M. B., Spellman, P. T., Brown, P. O. & Botstein, D. (1998) *Proc Natl Acad Sci U S A* **95,** 14863-8) was used to perform average linkage clustering of both genes and arrays, using median centering and normalization, and the results were displayed using TREEVIEW (Eisen, M. B., Spellman, P. T., Brown, P. O. & Botstein, D. (1998) *Proc Natl Acad Sci U S A* **95,** 14863-8). This organizes all of the data elements into a single tree with the higher levels of the tree representing the discovered classes. A threshold of 0 units was imposed before clustering because the negative values may contribute to artifacts. After this preprocessing, a set of genes was selected for clustering. For Dataset A, a variation filter was used that required a standard deviation greater than or equal to 50 expression units across samples, and 3,312 genes were selected. More stringent variation filters were selected (as few as 900 genes), which produced similar clustering results. For dataset B, 675 genes were selected based on the replicate filtering described above.

[00116] In summary, a hierarchical clustering was performed on two data sets: Dataset A, with 203 samples, and a subset, Dataset B, with 156 samples. Two distinct gene

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selections were used (3,312 genes selected by standard deviation in Fig. 1 versus 675 genes selected by replication filtering. To compare the results of these analyses, the clusters defined in the adenocarcinomas were mapped onto a tree generated using 3,312 genes. Clusters C2, C3 and C4 of the adenocarcinomas form consistently in both analyses.

Probabilistic Clustering

[00117] In order to validate the taxonomy obtained by hierarchical clustering, a model-based probabilistic clustering was also used (Cheeseman, P. & Stutz, J. (1996) in *Advances in Knowledge Discovery and Data Mining*, eds. Fayyad, U. M., Piatetsky-Shapiro, G., Smyth, P. & Uthurasamy, R. (MIT Press, Cambridge), Titterington, D. M., Smith, A. F. & Makov, U. F. (1985) *Statistical Analysis of Finite Mixture Distributions* (John Wiley, New York)), and the number and composition of clusters obtained by the two methods were compared. The specific program used for probabilistic clustering is AutoClass (Cheeseman, P. & Stutz, J. (1996) in *Advances in Knowledge Discovery and Data Mining*, eds. Fayyad, U. M., Piatetsky-Shapiro, G., Smyth, P. & Uthurasamy, R. (MIT Press, Cambridge). The method allows for the automatic selection of the number of clusters, and it performs a *soft* partitioning of the data, whereby each sample can be fractionally assigned to more than one cluster, thus reflecting the inherent uncertainty in the data (in practice, in all experiments samples were assigned to a cluster with probability 1). Probabilistic model-based clustering, usually referred to as finite-mixture models (Titterington, D. M., Smith, A. F. & Makov, U. F. (1985) *Statistical Analysis of Finite Mixture Distributions* (John Wiley, New York)), is built on the assumption that the observed data can be partitioned into sub-populations (clusters), each governed by a distinct probability distribution. Since *a priori* the cluster membership is not known, the resulting distribution of the observed data is a *mixture* of the sub-population distributions. Learning, or inducing, the probabilistic model generating the observed data thus entails determining the number of clusters (*model selection*), as well as the parameters of the sub-population distributions (*parameter estimation*). The model selection is based on a Bayesian score that measures the posterior probability of the model given the observed data. Assuming all models are *a priori* equally likely, this translates into searching for the model that assigns the highest probability to the observed data (i.e which best "explains" the data). It should be emphasized that the Bayesian score incorporates a component that penalizes model complexity (the higher the number of clusters, the higher the complexity of the model), thus automatically controlling for over-fitting. The parameter estimation for this type of modelling is a combinatorial optimization problem for which an

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exact solution is computationally infeasible. Therefore, an approximate solution needs to be adopted. AutoClass adopts the Expectation-Maximization algorithm (EM), an iterative procedure that, starting from a random initialization of the parameters, incrementally adjusts them in an attempt to find their maximum likelihood estimates (under rather general conditions, the procedure is guaranteed to converge to a local maximum) (Dempster, A. P., Laird, N. M. & Rubin, D. B. (1977) *J Royal Stat Soc* **39**, 398-409, McLachlan, G. J. & Krishnan, T. (1997) *The EM Algorithm and Extensions* (John Wiley, New York). It is important to point out that because of this random component in the estimation procedure, different runs of the learning algorithms may yield different results (i.e., different parameters – and consequently, different numbers of clusters – may be selected), a variability that is accounted for in the experimental evaluation.

Experimental Evaluation of Probabilistic Clustering

[00118] A model-based probabilistic clustering was applied to a data set of 156 samples (Dataset B). For the selection of the genes, the replicate filtering method was used as described above. Two feature sets were used, the first including 675 genes (obtained by setting the correlation threshold at 0.8), and the second including 1514 genes (correlation threshold setting of 0.7). The use of different feature sets was aimed at testing for the sensitivity of the clustering procedure to the number of genes included. AutoClass was then applied to the resulting data set. For each feature set, two sets of experiments were run. In the first experiment (Experiment 1), the learning algorithms were run 200 times, with the only difference between successive runs being in the random initialization of the model parameters. The aim of this experiment was to try to account for variability due to the approximate nature of the estimation procedure. In the second experiment (Experiment 2), the learning algorithms were run 200 times on "bootstrapped" data sets, where a bootstrapped data set was obtained by randomly picking, with replacement, 156 samples from the original data set. The bootstrapped data set differs from the original one in that some of the samples may appear in it multiple times, while other samples may be missing altogether. This experiment was aimed at testing for the robustness of the clustering results to random variations in the observed data. Fig. 6 shows the distribution of the number of clusters over multiple runs for the different settings. As expected, the variability in the number of clusters over multiple iterations was higher in Experiment 2 (bootstrapping) than in Experiment 1 (random restart). This was due to the fact that in a bootstrapped data set, it often happens that the same sample is included more than once (on average, over 200 iterations, each bootstrap

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data set contained about 100 of the 156 samples in the original data set. In other words, on average 56 samples were duplications of samples already included). If a sample was included a sufficient number of times, the clustering algorithm may find it appropriate to define a cluster for that sample only, thus artificially inflating the number of clusters. Despite this variability, it was reassuring to see that this alternative clustering methodology selected a number of clusters mostly varying between 6 and 9, very close to the number of clusters selected by hierarchical clustering.

[00119] A visualization method was used to control for the consistency of the cluster composition over multiple runs, as well as to compare the clusters found by AutoClass with the ones obtained by hierarchical clustering. A colored matrix that is a color-based rendition of a corresponding symmetric matrix whose entries record a normalized measure of how often two samples appear in the same cluster across multiple runs. Rows and columns in this matrix were indexed by the samples in the data set, thus yielding a 156×156 matrix, with each entry taking a real value between 0 and 1. An entry set to 0 (1) indicates that the two samples indexing that entry never (always) appear in the same cluster. More specifically, given two samples, the corresponding entry in the matrix records the quantity N_{match}/N_{total}, where N_{total} is the number of iterations in which both samples are included, and N_{match} denotes the number of iterations in which the two samples are included and are clustered together. That N_{total} is equal to the total number of iterations in Experiment 1, but not in Experiment 2, where it can often happen that a sample is not selected at all in a given iteration.

[00120] Ideally, all entries in the matrix are either 0 or 1, corresponding to the situation where the cluster composition remains unchanged over multiple runs of the algorithm. Furthermore, if the samples are arranged in the matrix in the order produced by hierarchical clustering, a perfect agreement between the two clustering methodologies would translate into a block-diagonal matrix with blocks of 1's along the diagonal – each block corresponding to a different cluster – surrounded by 0's. Two-dimensional matrices were generated corresponding, respectively, to Experiment 1 (200 iterations with random restart on the original data set) and Experiment 2 (200 iterations on bootstrap data sets) for the 675-gene data set. Corresponding two-dimensional matrices were generated for the 1514-gene data set. Blocks corresponding to the candidate clusters are clearly distinguishable along the diagonal in all four of the two-dimensional matrices, thus providing supporting evidence that the selected clusters were unaffected by random variations in the data set.

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K-Nearest Neighbor-based Marker Gene Selection and Supervised Learning

[00121] Following definition of "classes" and their boundaries, a *k*-NN algorithm was used to choose "marker" genes whose expression best correlated with each class distinction. Class definitions were based on clustering. Marker genes were chosen based on the signal-to-noise statistic $(M_{class0} - M_{class1})/(_{class0} + _{class1})$, where M and represent the mean and standard deviation of expression, respectively, for each class (Golub, T. R., Slonim, D. K., Tamayo, P., Huard, C., Gaasenbeek, M., Mesirov, J. P., Coller, H., Loh, M. L., Downing, J. R., Caligiuri, M. A., et al. (1999) *Science* **286,** 531-7).

[00122] As a further test of the relative robustness of the sample clusters, a supervised classifier was built using the following methodology. Following marker gene selection, a classifier was built and evaluated through leave-one-out cross-validation. For each round of cross-validation, one sample was withheld and the remaining samples were used to build a "*k*-NN" classifier (see below), from which class membership of the withheld sample was predicted. The top 25 genes selected by signal-to-noise metric for each class are shown in Table 9.

[00123] A weighted implementation of the *k*-NN algorithm that predicts the class of a new sample by selecting the calculating the Euclidean distance (d) of this sample to the *k* "nearest neighbor" samples in "expression" space in the training set was used, and the predicted class was selected to be that of the majority of the *k* samples (Dasarathy, V. B. (1991), (IEEE Computer Society Press, Los Alamitos, Calif.)). A marker gene selection process was performed by feeding the *k*-NN algorithm only the features with higher correlation with the target class. In this version of the algorithm the weight of each of the *k* neighbors was weighted according to 1/d.

[00124] The cross-validation step was repeated for each sample and the errors were tallied. A random 8-class classifier would be expected to give an error rate of 100-(100/8), or 87.5%. For the initial validation of clusters, classifiers were built with various numbers of marker genes selected from the 675-gene set that was used for hierarchical clustering. The best model used 100 genes (13 % overall error); however, models using 75-200 genes performed with less than 20% overall error.

[00125] For testing whether the cluster definitions were highly dependent on the 675-gene set, classifiers were built from the remaining 11,925 genes. The genes were passed through a variation filter and marker genes were selected as above. A 100-gene model gave an overall error rate of 26%, with the classes that represent clusters performing better than the "other" class.

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Kaplan-Meier Analysis and Permutation Testing.

[00126] Kaplan-Meier curves were generated using standard functions in S-PLUS package (Venables, W. N. & Ripley, B. D. (1998) *Modern applied statistics with S-PLUS* (Springer, Berlin)). Only 125 adenocarcinoma samples were used with survival information from adenocarcinoma samples. For each cluster, survival within-clusters was compared to the out-of-cluster group using the two-sample comparison based on the corresponding two K-M curves. In this way 5 K-M plots was obtained for each cluster, of which two plots have significant *P*-values for the comparison of the two curves, namely cluster 2 (C2, P =0.00476) and cluster 4 (C4, P=0.049). A similar analysis performed for stage I patient samples was statistically non-significant for all clusters. The small sample size (n=4) is a possible factor in the non-significance of the result for Stage I C2 patients.

[00127] These apparently significant *P*-values have a bias because of multiple hypothesis testing. To test for this selection bias, the cluster labels were randomly permuted among the samples and K-M significance, for each cluster, the within-cluster and out-of-cluster K-M curves and the corresponding *P*-values were re-computed. This randomization was repeated 1000 times. The 1000 sets of *P*-values were used to construct the null distributions for the test statistic T1= the smallest *P*-value among 5 clusters. From the 1000 permutations, the *P*-values for T1 = 0.044. This *P*-value is a reasonable assessment of the significance of outcome differences for the cluster C2 (Fig. 1). This statistical evidence supports the predictive value of C2 on survival.

Example 3: Gene markers for different lung cancers and adenocarcinoma sub-classes

[00128] Expression data were preprocessed by setting a minimal level of 10 units and only genes that showed 5-fold change across the data set were analyzed further. Genes correlated with a particular cluster labels (e.g. "c0" or "colon") were identified by sorting all of the genes on the array according the signal-to-noise statistic (mu_c0 - mu_others)/(sd_c0 + sd_others), where mu and sd represent the mean and standard deviation of expression, respectively, for each class.

[00129] Permutation of the column (sample) labels was performed to compare these correlations to what would be expected by chance. The top signal-to-noise scores for top marker genes were compared and compared with the corresponding ones for random permutation version of the cluster labels. 1000 random permutations were used to build histograms for the top marker, the second best, etc. Based on this histogram the 0.1% significance levels were estimated as compared with the values obtained for the real dataset.

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This test helps to assess the statistical significance of gene markers in terms of target class-correlations.

[00130] Included in the list of genes are those that exceed the 0.1% significance level for each cluster. For those clusters (colon, normal, C4) for which the lists are very long, only the top 200 genes are shown. The following Tables 1-8 present genes for the C1-C4 subclasses, normal, colorectal metastases, C0, and other subclasses. (The s2n_obs is the observed signal to noise value; the non_norm_list is the Affymetrix reference identifier; the LL_num is the LocusLink identifier; and Desc is the description of the gene or gene product.

Table 1: C1 Markers

[00131] According to the invention, preferred markers are markers 1-30, preferably 1-20, and more preferably 1-10.

Class C1

	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
1	1.29	1.024	36457_at	U10860	Hs.5398	8833	guanine monphosphate synthetase
2	1.25	0.865	40117_at	D84557	Hs.155462	4175	minichromosome maintenance deficient (mis5, S. pombe) 6
3	1.22	0.797	37337_at	AI803447	Hs.77496	6637	small nuclear ribonucleoprotein polypeptide G
4	1.18	0.770	1055_g_at	M87339	Hs.35120	5984	replication factor C (activator 1) 4 (37kD)
5	1.18	0.767	41547_at	AF047472	Hs.40323	9184	BUB3 (budding uninhibited by benzimidazoles 3, yeast) homolog
6	1.17	0.763	38840_s_at	L10678	Hs.91747	5217	profilin 2
7	1.12	0.757	38065_at	X62534	Hs.80684	3148	high-mobility group (nonhistone chromosomal) protein 2
8	1.11	0.754	709_at	J00314	Hs.336780	7280	tubulin, beta polypeptide
9	1.1	0.739	41583_at	AC004770	Hs.4756	2237	flap structure-specific endonuclease 1

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
10	1.06	0.731	40195_at	X14850	Hs.147097	3014	H2A histone family, member X
11	1.05	0.728	39109_at	AB024704	Hs.9329	22974	chromosome 20 open reading frame 1
12	1.05	0.727	207_at	M86752	Hs.75612	10963	stress-induced-phosphoprotein 1 (Hsp70/Hsp90-organizing protein)
13	1.05	0.722	1884_s_at	M15796	Hs.78996	5111	proliferating cell nuclear antigen
14	1.04	0.716	34763_at	AF020043	Hs.24485	9126	chondroitin sulfate proteoglycan 6 (bamacan)
15	1.02	0.715	40619_at	M91670	Hs.174070	27338	ubiquitin carrier protein
16	1.01	0.715	1824_s_at	J05614			proliferating cell nuclear antigen (PCNA)
17	1.01	0.714	572_at	M86699	Hs.169840	7272	TTK protein kinase
18	1	0.711	151_s_at	V00599	Hs.179661	2280	V00599 /FEATURE=mRNA /DEFINITION=HSTUB2 Human mRNA fragment encoding beta-tubulin. (from clone D-beta-1)
19	1	0.708	1803_at	X05360	Hs.184572	983	cell division cycle 2, G1 to S and G2 to M
20	0.99	0.706	1515_at	HG4074-HT4344			Rad2
21	0.98	0.704	34791_at	X52882	Hs.4112	6950	t-complex 1
22	0.97	0.702	40690_at	X54942	Hs.83758	1164	CDC28 protein kinase 2
23	0.96	0.700	40697_at	X51688	Hs.85137	890	cyclin A2
24	0.96	0.696	37686_s_at	Y09008	Hs.78853	7374	uracil-DNA glycosylase
25	0.96	0.693	982_at	X74795	Hs.77171	4174	minichromosome maintenance deficient (S. cerevisiae) 5 (cell division cycle 46)

BNSDOCID: <WO_____03029273A2_I_>

	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
26	0.95	0.692	1505_at	D00596	Hs.82962	7298	thymidylate synthetase
27	0.94	0.690	38992_at	X64229	Hs.110713	7913	DEK oncogene (DNA binding)
28	0.94	0.690	33255_at	M97856	Hs.243886	4678	nuclear autoantigenic sperm protein (histone-binding)
29	0.94	0.688	36813_at	U96131	Hs.6566	9319	thyroid hormone receptor interactor 13
30	0.93	0.684	34882_at	Y12065	Hs.296585	10528	nucleolar protein (KKE/D repeat)
31	0.91	0.684	34715_at	U74612	Hs.239	2305	forkhead box M1
32	0.9	0.683	674_g_at	J04031	Hs.172665	4522	methylenetetrahydrofolate dehydrogenase (NADP+ dependent), methenyltetrahydrofolate cyclohydrolase, formyltetrahydrofolate synthetase
33	0.9	0.680	39337_at	M37583	Hs.119192	3015	H2A histone family, member Z
34	0.89	0.679	41756_at	AJ010842	Hs.18259	11321	XPA binding protein 1; putative ATP(GTP)-binding protein
35	0.89	0.678	40417_at	D43950			chaperonin containing TCP1, subunit 5 (epsilon)
36	0.89	0.677	571_at	M86667	Hs.179662	4673	nucleosome assembly protein 1-like 1
37	0.89	0.676	38804_at	AF053641	Hs.90073	1434	chromosome segregation 1 (yeast homolog)-like
38	0.88	0.675	37304_at	U35451	Hs.77254	10951	chromobox homolog 1 (Drosophila HP1 beta)
39	0.88	0.674	34383_at	AB014458	Hs.35086	7398	ubiquitin specific protease 1

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
40	0.87	0.674	2003_s_at	U28946	Hs.3248	2956	mutS (E. coli) homolog 6
41	0.87	0.673	40407_at	U28386	Hs.159557	3838	karyopherin alpha 2 (RAG cohort 1, importin alpha 1)
42	0.87	0.672	40041_at	AF017790	Hs.58169	10403	highly expressed in cancer, rich in leucine heptad repeats
43	0.85	0.668	41375_at	AJ245416	Hs.103106	57819	U6 snRNA-associated Sm-like protein
44	0.85	0.666	1985_s_at	X73066	Hs.118638	4830	non-metastatic cells 1, protein (NM23A) expressed in
45	0.85	0.664	36987_at	M94362	Hs.334709	3999	lamin B2
46	0.84	0.663	1782_s_at	M31303	Hs.81915	3925	leukemia-associated phosphoprotein p18 (stathmin)
47	0.84	0.659	35699_at	AF053306	Hs.36708	701	budding uninhibited by benzimidazoles 1 (yeast homolog), beta
48	0.84	0.658	38414_at	U05340	Hs.82906	991	CDC20 (cell division cycle 20, S. cerevisiae, homolog)
49	0.84	0.657	35218_at	AF022385	Hs.28866	11235	programmed cell death 10
50	0.84	0.656	40726_at	U37426	Hs.8878	3832	kinesin-like 1
51	0.83	0.653	1136_at	L16991	Hs.79006	1841	deoxythymidylate kinase (thymidylate kinase)
52	0.83	0.652	36098_at	M72709	Hs.73737	6426	splicing factor, arginine/serine-rich 1 (splicing factor 2, alternate splicing factor)
53	0.83	0.650	38350_f_at	AF005392	Hs.98102	7278	tubulin, alpha 2
54	0.83	0.649	39374_at	AL022325	Hs.122552	51512	hypothetical protein FLJ10140

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
55	0.83	0.649	34314_at	X59543	Hs.2934	6240	ribonucleotide reductase M1 polypeptide
56	0.83	0.648	38473_at	M63180	Hs.84131	6897	threonyl-tRNA synthetase
57	0.83	0.647	1945_at	M25753	Hs.23960	891	cyclin B1
58	0.83	0.646	37347_at	AA926959	Hs.77550	84722	hypothetical protein MGC1780
59	0.82	0.645	40587_s_at	AF054186	Hs.298581	9521	eukaryotic translation elongation factor 1 epsilon 1
60	0.82	0.645	41342_at	D38076	Hs.24763	5902	RAN binding protein 1
61	0.82	0.645	860_at	U03911	Hs.78934	4436	mutS (E. coli) homolog 2 (colon cancer, nonpolyposis type 1)
62	0.82	0.643	41569_at	AI680675	Hs.44131	23234	KIAA0974 protein
63	0.82	0.642	32610_at	X93510	Hs.79691	8572	LIM domain protein
64	0.81	0.639	33247_at	U86782	Hs.178761	10213	26S proteasome-associated pad1 homolog
65	0.81	0.638	32530_at	X56468	Hs.74405	10971	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, theta polypeptide
66	0.81	0.638	1854_at	X13293	Hs.179718	4605	v-myb avian myeloblastosis viral oncogene homolog-like 2
67	0.81	0.637	37333_at	X63692	Hs.77462	1786	DNA (cytosine-5-)-methyltransferase 1
68	0.8	0.637	318_at	D64142	Hs.109804	8971	H1 histone family, member X
69	0.8	0.636	418_at	X65550	Hs.80976	4288	antigen identified by monoclonal antibody Ki-67
70	0.8	0.635	38116_at	D14657	Hs.81892	9768	KIAA0101 gene product

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
71	0.8	0.634	40638_at	X70944	Hs.180610	6421	splicing factor proline/glutamine rich (polypyrimidine tract-binding protein-associated)
72	0.8	0.633	36913_at	U75679	Hs.75257	7884	Hairpin binding protein, histone
73	0.79	0.631	36171_at	AI521453	Hs.74861	10923	activated RNA polymerase II transcription cofactor 4
74	0.79	0.631	38251_at	AI127424	Hs.90318	4632	myosin, light polypeptide 1, alkali; skeletal, fast
75	0.79	0.631	32214_at	AF003938	Hs.18792	9352	thioredoxin-like, 32kD
76	0.79	0.630	35312_at	D21063	Hs.57101	4171	minichromosome maintenance deficient (S. cerevisiae) 2 (mitotin)
77	0.79	0.630	35995_at	AF067656	Hs.42650	11130	ZW10 interactor
78	0.79	0.626	39677_at	D80008	Hs.36232	9837	KIAA0186 gene product
79	0.78	0.624	38031_at	D21853	Hs.79768	9775	KIAA0111 gene product
80	0.78	0.624	34327_at	Z46606			HLTF gene for helicase-like transcription factor /cds=UNKNOWN /gb=Z46606 /gi=575250 /ug=Hs.3068 /len=5439
81	0.78	0.623	41322_s_at	AI816034	Hs.23990	55651	nucleolar protein family A, member 2 (H/ACA small nucleolar RNPs)
82	0.78	0.622	36941_at	U16954	Hs.75823	10962	ALL1-fused gene from chromosome 1q
83	0.78	0.621	37228_at	U01038	Hs.77597	5347	polo (Drosophia)-like kinase

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
84	0.78	0.620	140_s_at	U68063	Hs.30035	6434	splicing factor, arginine/serine-rich (transformer 2 Drosophila homolog) 10
85	0.77	0.620	149_at	U90426	Hs.179606	10212	nuclear RNA helicase, DECD variant of DEAD box family
86	0.77	0.620	349_g_at	D14678	Hs.20830	3833	kinesin-like 2
87	0.77	0.619	1599_at	L25876	Hs.84113	1033	cyclin-dependent kinase inhibitor 3 (CDK2-associated dual specificity phosphatase)
88	0.77	0.619	39056_at	X53793	Hs.117950	10606	multifunctional polypeptide similar to SAICAR synthetase and AIR carboxylase
89	0.77	0.618	32594_at	AF026291	Hs.79150	10575	chaperonin containing TCP1, subunit 4 (delta)
90	0.77	0.618	37985_at	L37747			lamin B1
91	0.77	0.618	584_s_at	M30938	Hs.84981	7520	X-ray repair complementing defective repair in Chinese hamster cells 5 (double-strand-break rejoining; Ku autoantigen, 80kD)
92	0.77	0.618	34659_at	AB018334	Hs.23255	9631	nucleoporin 155kD
93	0.77	0.616	39812_at	X79865	Hs.109059	6182	mitochondrial ribosomal protein L12
94	0.77	0.615	41403_at	AI032612	Hs.105465	6636	small nuclear ribonucleoprotein polypeptide F
95	0.76	0.615	33252_at	D38073	Hs.179565	4172	minichromosome maintenance deficient (S. cerevisiae) 3

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
96	0.76	0.614	37738_g_at	D25547	Hs.79137	5110	protein-L-isoaspartate (D-aspartate) O-methyltransferase
97	0.76	0.614	35916_s_at	AA877215			cDNA, 3 end
98	0.75	0.613	32843_s_at	M30448			casein kinase 2, beta polypeptide
99	0.75	0.613	1674_at	M15990	Hs.194148	7525	v-yes-1 Yamaguchi sarcoma viral oncogene homolog 1
100	0.74	0.611	40842_at	M60784			small nuclear ribonucleoprotein polypeptide A
101	0.74	0.610	38847_at	D79997	Hs.184339	9833	KIAA0175 gene product
102	0.74	0.609	39965_at	AI570572	Hs.45002	5881	ras-related C3 botulinum toxin substrate 3 (rho family, small GTP binding protein Rac3)
103	0.74	0.609	351_f_at	D28423			pre-mRNA splicing factor SRp20, 5"UTR
104	0.73	0.607	36135_at	U86602	Hs.74407	10969	nucleolar protein p40; homolog of yeast EBNA1-binding protein
105	0.73	0.607	39076_s_at	AI991040	Hs.334879	10589	DR1-associated protein 1 (negative cofactor 2 alpha)
106	0.73	0.606	34878_at	AB019987	Hs.50758	10051	SMC4 (structural maintenance of chromosomes 4, yeast)-like 1
107	0.73	0.604	41855_at	AF030424	Hs.13340	8520	histone acetyltransferase 1
108	0.73	0.604	38792_at	AD001528	Hs.89718	6611	spermine synthase
109	0.72	0.602	38123_at	D14878	Hs.82043	8872	D123 gene product
110	0.72	0.602	40145_at	AI375913	Hs.156346	7153	topoisomerase (DNA) II alpha (170kD)
111	0.72	0.601	39262_at	U79266	Hs.23642	29901	protein predicted by clone 23627

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
112	0.72	0.600	36107_at	AA845575	Hs.73851	522	ATP synthase, H+ transporting, mitochondrial F0 complex, subunit F6
113	0.72	0.599	37305_at	U61145	Hs.77256	2146	enhancer of zeste (Drosophila) homolog 2
114	0.72	0.599	34380_at	AC004472	Hs.3439	30968	stomatin-like 2
115	0.72	0.599	276_at	L08069	Hs.94	3301	heat shock protein, DNAJ-like 2
116	0.72	0.599	34795_at	U84573	Hs.41270	5352	procollagen-lysine, 2-oxoglutarate 5-dioxygenase (lysine hydroxylase) 2
117	0.71	0.599	39969_at	AA255502	Hs.46423	8364	H4 histone family, member G
118	0.71	0.599	32844_at	AF104913	Hs.211568	1981	eukaryotic translation initiation factor 4 gamma, 1
119	0.71	0.599	41407_at	L03411	Hs.106061	7936	RD RNA-binding protein
120	0.71	0.598	39759_at	AL031781	Hs.15020	9444	homolog of mouse quaking QKI (KH domain RNA binding protein)
121	0.71	0.598	35364_at	U50939	Hs.61828	8883	amyloid beta precursor protein-binding protein 1, 59kD
122	0.71	0.598	36812_at	U92715	Hs.6564	8412	breast cancer anti-estrogen resistance 3
123	0.71	0.598	36837_at	U63743	Hs.69360	11004	kinesin-like 6 (mitotic centromere-associated kinesin)
124	0.71	0.597	471_f_at	U47634	Hs.159154	10381	tubulin, beta, 4
125	0.71	0.597	40879_at	AB014599	Hs.330988	23299	KIAA0699 protein
126	0.71	0.596	947_at	D55716	Hs.77152	4176	minichromosome maintenance deficient (S. cerevisiae) 7

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
127	0.71	0.595	157_at	U65011	Hs.30743	23532	preferentially expressed antigen in melanoma
128	0.7	0.593	35200_at	X92518	Hs.2726	8091	high-mobility group (nonhistone chromosomal) protein isoform I-C
129	0.7	0.592	32194_at	M37197	Hs.184760	10153	CCAAT-box-binding transcription factor
130	0.7	0.592	39173_at	X56597	Hs.99853	2091	fibrillarin
131	0.7	0.590	1840_g_at	HG1112-HT1112			Ras-Like Protein Tc4
132	0.7	0.588	37739_at	M86737	Hs.79162	6749	structure specific recognition protein 1
133	0.7	0.587	34510_at	AF070552	Hs.122908	81620	DNA replication factor
134	0.7	0.585	36536_at	AF070614	Hs.61490	29970	schwannomin interacting protein 1
135	0.7	0.583	36863_at	AF032862	Hs.72550	3161	hyaluronan-mediated motility receptor (RHAMM)
136	0.69	0.583	34790_at	S70154	Hs.278544	39	acetyl-Coenzyme A acetyltransferase 2 (acetoacetyl Coenzyme A thiolase)
137	0.69	0.583	527_at	U14518	Hs.1594	1058	centromere protein A (17kD)
138	0.69	0.581	38679_g_at	AA733050	Hs.1066	6635	small nuclear ribonucleoprotein polypeptide E
139	0.69	0.581	39984_g_at	U73704	Hs.49105	11146	FKBP-associated protein
140	0.68	0.581	40610_at	AI743507	Hs.173518	51663	likely ortholog of mouse zinc finger protein Zfr
141	0.68	0.581	39792_at	AF000364	Hs.15265	10236	heterogeneous nuclear ribonucleoprotein R
142	0.68	0.579	33266_at	AF015254	Hs.180655	9212	serine/threonine kinase 12

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
143	0.68	0.578	31858_at	X07315	Hs.151734	10204	nuclear transport factor 2 (placental protein 15)
144	0.68	0.578	32340_s_at	M85234	Hs.74497	4904	nuclease sensitive element binding protein 1
145	0.68	0.577	34099_f_at	W26056	Hs.343569		cDNA
146	0.68	0.577	831_at	U28042	Hs.41706	1662	DEAD/H (Asp-Glu-Ala-Asp/His) box polypeptide 10 (RNA helicase)
147	0.68	0.576	37945_at	U91316	Hs.8679	11332	cytosolic acyl coenzyme A thioester hydrolase
148	0.68	0.576	33035_at	AL021397	Hs.137576	26514	ribosomal protein L34 pseudogene 1
149	0.68	0.575	32120_at	AF063308	Hs.16244	10615	mitotic spindle coiled-coil related protein
150	0.68	0.575	36104_at	AA526497	Hs.73818	7388	ubiquinol-cytochrome c reductase hinge protein
151	0.67	0.575	32548_at	L24804	Hs.278270	10728	unactive progesterone receptor, 23 kD
152	0.67	0.574	36872_at	AL120559	Hs.7351	10776	cyclic AMP phosphoprotein, 19 kD
153	0.67	0.573	38634_at	M11433	Hs.101850	5947	retinol-binding protein 1, cellular
154	0.67	0.573	37683_at	D80012	Hs.78829	9100	ubiquitin specific protease 10
155	0.67	0.573	33127_at	U89942	Hs.83354	4017	lysyl oxidase-like 2
156	0.67	0.572	41401_at	U57646	Hs.10526	1466	cysteine and glycine-rich protein 2
157	0.67	0.572	40074_at	X16396	Hs.154672	10797	methylene tetrahydrofolate dehydrogenase (NAD+ dependent), methenyltetrahydrofolate cyclohydrolase

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
158	0.66	0.572	41600_at	U59435	Hs.5181	5036	proliferation-associated 2G4, 38kD
159	0.66	0.571	1449_at	D00763	Hs.251531	5685	proteasome (prosome, macropain) subunit, alpha type, 4
160	0.66	0.570	37046_at	AI246726	Hs.76913	5686	proteasome (prosome, macropain) subunit, alpha type, 5
161	0.66	0.570	34814_at	AL041443	Hs.4311	10054	SUMO-1 activating enzyme subunit 2
162	0.66	0.570	32615_at	J05032	Hs.80758	1615	aspartyl-tRNA synthetase
163	0.66	0.569	39086_g_at	AA768912	Hs.923	6742	single-stranded DNA-binding protein 1
164	0.65	0.569	39747_at	U52427	Hs.14839	5436	polymerase (RNA) II (DNA directed) polypeptide G
165	0.65	0.568	39009_at	N98670			cDNA, 5 end
166	0.65	0.568	40124_at	Y18418	Hs.272822	8607	RuvB (E coli homolog)-like 1
167	0.65	0.568	32730_at	AL080059	Hs.173094	85453	Homo sapiens mRNA for KIAA1750 protein, partial cds
168	0.64	0.567	38662_at	AL047596	Hs.306117	23152	KIAA0306 protein
169	0.64	0.567	33679_f_at	X02344	Hs.251653	10383	tubulin, beta, 2
170	0.64	0.567	37302_at	U30872	Hs.77204	1063	centromere protein F (350/400kD, mitosin)
171	0.64	0.566	39704_s_at	L17131	Hs.139800	3159	high-mobility group (nonhistone chromosomal) protein isoforms I and Y
172	0.64	0.565	131_at	X83928	Hs.83126	6882	TATA box binding protein (TBP)-associated factor, RNA polymerase II, I, 28kD

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
173	0.64	0.565	40779_at	U59919	Hs.171374	22920	smg GDS-ASSOCIATED PROTEIN
174	0.64	0.564	38114_at	D38551	Hs.81848	5885	RAD21 (S. pombe) homolog
175	0.64	0.564	32850_at	Z25535	Hs.211608	9972	nucleoporin 153kD
176	0.64	0.564	1250_at	U47077	Hs.155637	5591	protein kinase, DNA-activated, catalytic polypeptide
177	0.64	0.564	37345_at	AF013759	Hs.7753	813	calumenin
178	0.64	0.563	37293_at	D43948	Hs.76989	9793	KIAA0097 gene product
179	0.64	0.563	40418_at	X74262	Hs.16003	5928	retinoblastoma-binding protein 4
180	0.64	0.562	38158_at	D79987	Hs.153479	9700	extra spindle poles, S. cerevisiae, homolog of
181	0.64	0.562	910_at	M15205	Hs.105097	7083	thymidine kinase 1, soluble
182	0.64	0.562	35314_at	D63880	Hs.5719	9918	chromosome condensation-related SMC-associated protein 1
183	0.64	0.561	41601_at	AA142964	Hs.64311	6868	a disintegrin and metalloproteinase domain 17 (tumor necrosis factor, alpha, converting enzyme)
184	0.63	0.561	41824_at	AI140114	Hs.6153	51096	CGI-48 protein
185	0.63	0.560	36184_at	L06419	Hs.75093	5351	procollagen-lysine, 2-oxoglutarate 5-dioxygenase (lysine hydroxylase, Ehlers-Danlos syndrome type VI)
186	0.63	0.560	41133_at	U32519	Hs.220689	10146	Ras-GTPase-activating protein SH3-domain-binding protein

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
187	0.63	0.559	35694_at	AB014587	Hs.3628	9448	mitogen-activated protein kinase kinase kinase kinase 4
188	0.63	0.559	39070_at	U03057	Hs.118400	6624	singed (Drosophila)-like (sea urchin fascin homolog like)
189	0.63	0.559	1801_at	U76638	Hs.54089	580	BRCA1 associated RING domain 1
190	0.63	0.557	38405_at	U25165	Hs.82712	8087	fragile X mental retardation, autosomal homolog 1
191	0.63	0.557	38684_at	AJ010953	Hs.106778	27032	ATPase, Ca++ transporting, type 2C, member 1
192	0.63	0.554	31832_at	AB006624	Hs.14912	23306	KIAA0286 protein
193	0.63	0.554	410_s_at	X57152	Hs.165843	1460	casein kinase 2, beta polypeptide
194	0.62	0.554	39060_at	D38048	Hs.118065	5695	proteasome (prosome, macropain) subunit, beta type, 7
195	0.62	0.553	40412_at	AA203476	Hs.252587	9232	pituitary tumor-transforming 1
196	0.62	0.552	37729_at	Y08614	Hs.79090	7514	exportin 1 (CRM1, yeast, homolog)
197	0.62	0.552	38863_at	L07540	Hs.171075	5985	replication factor C (activator 1) 5 (36.5kD)
198	0.62	0.551	37726_at	X06323	Hs.79086	11222	mitochondrial ribosomal protein L3
199	0.62	0.551	41003_at	U41816	Hs.91161	5203	prefoldin 4
200	0.62	0.550	592_at	M34079	Hs.250758	5702	proteasome (prosome, macropain) 26S subunit, ATPase, 3

Table 2: C2 Markers

[00132] The C2 class is a robust class of markers. According to the invention, preferred markers are markers 1-30, preferably 1-20, and more preferably 1-10. Highly

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preferred markers are kallikrein 11, achaete-scute complex (Drosophila) homolog-like 1, carboxypeptidase E, trefoil factor 3 (intestinal), calcitonin/calcitonin-related polypeptide alpha, proprotein convertase, dual specificity phosphatase 4, and dopa decarboxylase.

Class C2

	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
1	1.46	0.781	40035_at	AB012917	Hs.57771	11012	kallikrein 11
2	1.27	0.736	40544_g_at	L08424	Hs.1619	429	achaete-scute complex (Drosophila) homolog-like 1
3	1.27	0.721	36606_at	X51405	Hs.75360	1363	carboxypeptidase E
4	1.21	0.715	31477_at	L08044	Hs.82961	7033	trefoil factor 3 (intestinal)
5	1.18	0.708	36299_at	X02330			calcitonin/calcitonin-related polypeptide, alpha
6	1.17	0.699	40649_at	X64810	Hs.78977	5122	proprotein convertase subtilisin/kexin type 1
7	1.16	0.684	442_at	X15187	Hs.82689	7184	tumor rejection antigen (gp96) 1
8	1.05	0.660	36300_at	X15943	Hs.37058	796	calcitonin/calcitonin-related polypeptide, alpha
9	1.02	0.658	39332_at	AF035316	Hs.336780	7280	tubulin, beta polypeptide
10	0.97	0.651	39756_g_at	Z93930	Hs.149923	7494	X-box binding protein 1
11	0.96	0.647	39135_at	AB018310	Hs.95180	23151	KIAA0767 protein
12	0.95	0.645	34785_at	AB028948	Hs.4084	23389	KIAA1025 protein
13	0.92	0.644	37617_at	U90912	Hs.81897	54462	KIAA1128 protein
14	0.85	0.630	1788_s_at	U48807	Hs.2359	1846	dual specificity phosphatase 4
15	0.85	0.630	37928_at	AA621555	Hs.84928	4801	nuclear transcription factor Y, beta

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
16	0.84	0.625	37141_at	U39840	Hs.299867	3169	hepatocyte nuclear factor 3, alpha
17	0.84	0.623	35995_at	AF067656	Hs.42650	11130	ZW10 interactor
18	0.83	0.622	40201_at	M76180	Hs.150403	1644	dopa decarboxylase (aromatic L-amino acid decarboxylase)
19	0.82	0.620	35800_at	D63391	Hs.6793	5050	platelet-activating factor acetylhydrolase, isoform Ib, gamma subunit (29kD)
20	0.8	0.618	33543_s_at	U77718	Hs.44499	5411	pinin, desmosome associated protein
21	0.8	0.615	1822_at	HG4677-HT5102			Oncogene Ret/Ptc2, Fusion Activated
22	0.79	0.613	35343_at	M37400	Hs.597	2805	glutamic-oxaloacetic transaminase 1, soluble (aspartate aminotransferase 1)
23	0.78	0.610	41403_at	AI032612	Hs.105465	6636	small nuclear ribonucleoprotein polypeptide F
24	0.78	0.606	37426_at	U80736	Hs.110826	27324	trinucleotide repeat containing 9
25	0.77	0.605	39113_at	AI262789	Hs.93659	9601	protein disulfide isomerase related protein (calcium-binding protein, intestinal-related)
26	0.77	0.604	40881_at	X64330	Hs.174140	47	ATP citrate lyase
27	0.77	0.603	32137_at	AF029778	Hs.166154	3714	jagged 2

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
28	0.77	0.600	34690_at	U66616	Hs.236030	6601	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily c, member 2
29	0.77	0.599	41395_at	AB003791	Hs.104576	8534	carbohydrate (keratan sulfate Gal-6) sulfotransferase 1
30	0.76	0.599	39891_at	AI246730	Hs.126901		cDNA, 3 end
31	0.76	0.598	41250_at	U24169	Hs.301613	7965	JTV1 gene
32	0.76	0.598	37545_at	W22110	Hs.7934	9314	Kruppel-like factor 4 (gut)
33	0.75	0.597	41146_at	J03473	Hs.177766	142	ADP-ribosyltransferase (NAD+; poly (ADP-ribose) polymerase)
34	0.74	0.597	40865_at	U51166	Hs.173824	6996	thymine-DNA glycosylase
35	0.74	0.597	35147_at	AB002360	Hs.25515	23263	MCF.2 cell line derived transforming sequence-like
36	0.74	0.591	36847_r_at	AA121509	Hs.70830	51690	U6 snRNA-associated Sm-like protein LSm7
37	0.73	0.588	37293_at	D43948	Hs.76989	9793	KIAA0097 gene product
38	0.73	0.587	36482_s_at	Y15724	Hs.5541	489	ATPase, Ca++ transporting, ubiquitous
39	0.72	0.586	38654_at	X65488	Hs.103804	3192	heterogeneous nuclear ribonucleoprotein U (scaffold attachment factor A)
40	0.72	0.583	37359_at	D14658	Hs.77665	9789	KIAA0102 gene product

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
41	0.72	0.582	37638_at	D50857	Hs.82295	1793	dedicator of cyto-kinesis 1
42	0.72	0.582	39824_at	AI391564	Hs.110820		cDNA, 3 end
43	0.71	0.580	37019_at	J00129	Hs.7645	2244	fibrinogen, B beta polypeptide
44	0.71	0.578	40074_at	X16396	Hs.154672	10797	methylene tetrahydrofolate dehydrogenase (NAD+ dependent), methenyltetrahydrofolate cyclohydrolase
45	0.71	0.576	40584_at	Y08612	Hs.172108	4927	nucleoporin 88kD
46	0.7	0.576	33266_at	AF015254	Hs.180655	9212	serine/threonine kinase 12
47	0.69	0.575	36008_at	AF041434	Hs.43666	11156	protein tyrosine phosphatase type IVA, member 3
48	0.69	0.574	37333_at	X63692	Hs.77462	1786	DNA (cytosine-5-)-methyltransferase 1
49	0.69	0.574	1660_at	D83004	Hs.75355	7334	ubiquitin-conjugating enzyme E2N (homologous to yeast UBC13)
50	0.69	0.573	36149_at	D78014	Hs.74566	1809	dihydropyrimidinase-like 3
51	0.68	0.573	39692_at	AL080209	Hs.13659	64764	hypothetical protein DKFZp586F2423
52	0.68	0.570	40317_at	U57352	Hs.6517	40	amiloride-sensitive cation channel 1, neuronal (degenerin)
53	0.67	0.568	31906_at	AF068754	Hs.250899	3281	heat shock factor binding protein 1

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
54	0.67	0.567	149_at	U90426	Hs.179606	10212	nuclear RNA helicase, DECD variant of DEAD box family
55	0.67	0.567	38978_at	AF013758	Hs.109643	10605	polyadenylate binding protein-interacting protein 1
56	0.67	0.565	35566_f_at	AF015128	Hs.301365		IgG heavy chain variable region (Vh26)
57	0.66	0.564	36745_at	AF035308	Hs.167036		clone 23798 and 23825
58	0.66	0.563	36133_at	AL031058	Hs.74316	1832	desmoplakin (DPI, DPII)
59	0.66	0.563	35966_at	X71125	Hs.79033	25797	glutaminyl-peptide cyclotransferase (glutaminyl cyclase)
60	0.66	0.562	37955_at	AB015631	Hs.8752	10330	transmembrane protein 4
61	0.65	0.562	40846_g_at	U10324	Hs.256583	3609	interleukin enhancer binding factor 3, 90kD
62	0.65	0.560	37101_at	AL050008	Hs.306186	25855	DKFZP564A063 protein
63	0.65	0.559	40580_r_at	M24398	Hs.171814	5763	parathymosin
64	0.65	0.559	36489_at	D00860	Hs.56	5631	phosphoribosyl pyrophosphate synthetase 1
65	0.65	0.558	37133_at	AF027406	Hs.104865	26576	serine/threonine kinase 23
66	0.64	0.557	33714_at	Y10043	Hs.19114	3149	high-mobility group (nonhistone chromosomal) protein 4
67	0.64	0.557	35351_at	U89505	Hs.6106	5936	RNA binding motif protein 4
68	0.64	0.557	41829_at	AB018274	Hs.6214	23367	KIAA0731 protein

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
69	0.64	0.555	39158_at	AB021663	Hs.9754	22809	activating transcription factor 5
70	0.64	0.555	35163_at	AB028964	Hs.26023	22887	KIAA1041 protein
71	0.64	0.555	36406_at	AA401397	Hs.165296	26085	kallikrein 13
72	0.63	0.554	32149_at	AA532495	Hs.183752	4477	microseminoprotein, beta-
73	0.63	0.554	32825_at	Y10805	Hs.20521	3276	HMT1 (hnRNP methyltransferase, S. cerevisiae)-like 2
74	0.63	0.553	35590_s_at	X81832			gastric inhibitory polypeptide receptor
75	0.63	0.553	36636_at	M12267	Hs.75485	4942	ornithine aminotransferase (gyrate atrophy)
76	0.63	0.553	37944_at	U19523	Hs.86724	2643	GTP cyclohydrolase 1 (dopa-responsive dystonia)
77	0.63	0.552	41083_at	AC006276	Hs.99093		chromosome 19, cosmid R28379
78	0.62	0.550	39317_at	D86324	Hs.24697	8418	cytidine monophosphate-N-acetylneuraminic acid hydroxylase (CMP-N-acetylneuraminate monooxygenase)
79	0.62	0.550	33162_at	X02160	Hs.89695	3643	insulin receptor
80	0.62	0.549	31586_f_at	X72475	Hs.156110	3514	immunoglobulin kappa constant
81	0.62	0.549	34289_f_at	D50920	Hs.23106	9862	KIAA0130 gene product
82	0.62	0.549	36615_at	M83751	Hs.75412	7873	Arginine-rich protein

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
83	0.62	0.546	904_s_at	L47276			(cell line HL-60) alpha topoisomerase truncated-form mRNA, 3 UTR
84	0.62	0.545	39791_at	M23114	Hs.1526	488	ATPase, Ca++ transporting, cardiac muscle, slow twitch 2
85	0.62	0.544	36203_at	X16277	Hs.75212	4953	ornithine decarboxylase 1
86	0.61	0.544	1582_at	M29540	Hs.220529	1048	carcinoembryonic antigen-related cell adhesion molecule 5
87	0.61	0.544	38456_s_at	AL049650	Hs.83753	6628	small nuclear ribonucleoprotein polypeptides B and B1
88	0.61	0.544	39610_at	X16665	Hs.2733	3212	homeo box B2
89	0.61	0.544	37272_at	X57206	Hs.78877	3707	inositol 1,4,5-trisphosphate 3-kinase B
90	0.61	0.544	36185_at	D32050	Hs.75102	16	alanyl-tRNA synthetase
91	0.61	0.544	38435_at	U25182	Hs.83383	10549	thioredoxin peroxidase (antioxidant enzyme)
92	0.6	0.544	32447_at	U76388	Hs.157037	2516	nuclear receptor subfamily 5, group A, member 1
93	0.6	0.544	38753_at	AF039022	Hs.85951	11260	exportin, tRNA (nuclear export receptor for tRNAs)
94	0.6	0.543	38248_at	AB011124	Hs.90232	9762	KIAA0552 gene product
95	0.6	0.543	38719_at	U03985	Hs.108802	4905	N-ethylmaleimide-sensitive factor

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locusli nk or affy)
96	0.6	0.543	34105_f_at	AI147237	Hs.300697	3502	immunoglobulin heavy constant gamma 3 (G3m marker)
97	0.6	0.543	40840_at	M80254	Hs.173125	10105	peptidylprolyl isomerase F (cyclophilin F)
98	0.6	0.542	1745_at	HG4679-HT5104			Oncogene Ret/Ptc, Fusion Activated
99	0.59	0.542	1884_s_at	M15796	Hs.78996	5111	proliferating cell nuclear antigen
100	0.59	0.542	31935_s_at	U75968	Hs.27424	1663	DEAD/H (Asp-Glu-Ala-Asp/His) box polypeptide 11 (S.cerevisiae CHL1-like helicase)
101	0.59	0.542	34933_at	AJ238381	Hs.132576	5083	paired box gene 9
102	0.59	0.542	33304_at	U88964	Hs.183487	3669	interferon stimulated gene (20kD)
103	0.59	0.542	38340_at	AB014555	Hs.96731	9026	huntingtin interacting protein-1-related
104	0.58	0.542	1796_s_at	U05681			B-cell CLL/lymphoma 3
105	0.58	0.542	34726_at	U07139	Hs.250712	784	calcium channel, voltage-dependent, beta 3 subunit
106	0.58	0.541	35253_at	AB011143	Hs.30687	9846	GRB2-associated binding protein 2
107	0.58	0.541	35151_at	AF089814	Hs.25664	10263	tumor suppressor deleted in oral cancer-related 1

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
108	0.58	0.541	38635_at	Z69043	Hs.102135	6748	signal sequence receptor, delta (translocon-associated protein delta)
109	0.58	0.541	39040_at	W28360	Hs.184325	51632	CGI-76 protein
110	0.57	0.541	38860_at	U66346	Hs.189	5143	phosphodiesterase 4C, cAMP-specific (dunce (Drosophila)-homolog phosphodiesterase E1)
111	0.57	0.541	1432_s_at	D16105	Hs.210	4058	leukocyte tyrosine kinase
112	0.57	0.541	36851_g_at	U42360			Putative prostate cancer tumor suppressor
113	0.57	0.540	37985_at	L37747			lamin B1
114	0.57	0.540	38708_at	AF054183	Hs.10842	5901	RAN, member RAS oncogene family
115	0.57	0.540	32404_at	AF065314	Hs.234785	1261	cyclic nucleotide gated channel alpha 3
116	0.57	0.540	36970_at	D80004	Hs.75909	23199	KIAA0182 protein
117	0.57	0.540	32646_at	AB007918	Hs.169182	23046	KIAA0449 protein
118	0.57	0.539	32485_at	X00371	Hs.118836	4151	myoglobin
119	0.57	0.538	37774_at	AI819942	Hs.90998	23157	septin 2
120	0.57	0.538	36153_at	L13848	Hs.74578	1660	DEAD/H (Asp-Glu-Ala-Asp/His) box polypeptide 9 (RNA helicase A, nuclear DNA helicase II; leukophysin)
121	0.57	0.538	288_s_at	L25931	Hs.152931	3930	lamin B receptor
122	0.56	0.538	33347_at	AA883868	Hs.216354	6048	ring finger protein 5
123	0.56	0.538	33399_at	AA142942	Hs.241507	6194	ribosomal protein S6

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
124	0.56	0.538	1888_s_at	X06182	Hs.81665	3815	v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog
125	0.56	0.538	1846_at	L78132	Hs.4082	3964	prostate carcinoma tumor antigen (pcta-1)/ lectin
126	0.56	0.537	34338_at	D49738	Hs.31053	1155	cytoskeleton-associated protein 1
127	0.56	0.537	41241_at	D84273	Hs.181311	4677	asparaginyl-tRNA synthetase
128	0.56	0.536	35670_at	M37457			ATPase, Na+/K+ transporting, alpha 3 polypeptide
129	0.56	0.536	41399_at	AB029034	Hs.285641	23133	KIAA1111 protein
130	0.55	0.536	36676_at	AL031659	Hs.75722	6185	growth hormone releasing hormone
131	0.55	0.536	39927_at	U17032	Hs.267831	394	Rho GTPase activating protein 5
132	0.55	0.536	1257_s_at	L42379	Hs.77266	5768	quiescin Q6
133	0.55	0.535	37576_at	U52969	Hs.80296	5121	Purkinje cell protein 4
134	0.55	0.535	34987_s_at	X79536	Hs.249495	3178	heterogeneous nuclear ribonucleoprotein A1
135	0.55	0.535	1798_at	U41060	Hs.79136	25800	LIV-1 protein, estrogen regulated
136	0.55	0.535	40674_s_at	S82986	Hs.820	3223	homeo box C6
137	0.55	0.535	39342_at	X94754	Hs.279946	4141	methionine-tRNA synthetase

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
138	0.55	0.535	38707_r_at	S75174	Hs.108371	1874	E2F transcription factor 4, p107/p130-binding
139	0.55	0.535	34648_at	Z12830	Hs.250773	6745	signal sequence receptor, alpha (translocon-associated protein alpha)
140	0.54	0.535	40653_at	U32439	Hs.79348	6000	regulator of G-protein signalling 7
141	0.54	0.534	34827_at	AF045458	Hs.47061	8408	unc-51 (C. elegans)-like kinase 1
142	0.54	0.534	36178_at	U23143	Hs.75069	6472	serine hydroxymethyltransferase 2 (mitochondrial)
143	0.54	0.534	34264_at	AB026894	Hs.226499	23623	nesca protein
144	0.54	0.534	41750_at	D49489	Hs.182429	10130	protein disulfide isomerase-related protein
145	0.54	0.534	36971_at	D87446	Hs.75912	23505	KIAA0257 protein
146	0.54	0.534	38399_at	AL034428	Hs.82575	6629	small nuclear ribonucleoprotein polypeptide B"
147	0.54	0.534	32190_at	AL050118	Hs.184641	9415	fatty acid desaturase 2
148	0.54	0.534	38835_at	U94831	Hs.91586	10548	transmembrane 9 superfamily member 1
149	0.54	0.533	37316_r_at	AI057607	Hs.7731	55837	uncharacterized bone marrow protein BM036

Table 3: C3 Markers

[00133] **According** to the invention, preferred markers are markers 1-30, preferably 1-20, and more preferably 1-10.

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Class C3

	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
1	1.42	0.866	37669_s_at	U16799	Hs.78629	481	ATPase, Na+/K+ transporting, beta 1 polypeptide
2	1.2	0.724	36066_at	AB020635	Hs.4984	23382	KIAA0828 protein
3	1.17	0.707	33699_at	M18667			progastricsin (pepsinogen C)
4	1.06	0.706	1081_at	M33764	Hs.75212	4953	ornithine decarboxylase 1
5	1.06	0.688	33396_at	U12472	Hs.226795	2950	glutathione S-transferase pi
6	1.06	0.679	34319_at	AA131149	Hs.2962	6286	S100 calcium-binding protein P
7	1.02	0.674	40409_at	U46689	Hs.159608	224	aldehyde dehydrogenase 10 (fatty aldehyde dehydrogenase)
8	1.02	0.673	32805_at	U05861			aldo-keto reductase family 1, member C1 (dihydrodiol dehydrogenase 1; 20-alpha (3-alpha)-hydroxysteroid dehydrogenase)
9	0.99	0.667	33383_f_at	AI820718	Hs.250505	5914	retinoic acid receptor, alpha
10	0.98	0.663	35207_at	X76180	Hs.2794	6337	sodium channel, nonvoltage-gated 1 alpha
11	0.98	0.655	33052_at	U95301	Hs.144442	8399	phospholipase A2, group X
12	0.98	0.649	38526_at	U02882	Hs.172081	5144	phosphodiesterase 4D, cAMP-specific (dunce (Drosophila)-homolog phosphodiesterase E3)
13	0.97	0.646	38066_at	M81600			diaphorase (NADH/NADPH) (cytochrome b-5 reductase)
14	0.93	0.644	1882_g_at	HG4058-HT4328			Oncogene Aml1-Evi-1, Fusion Activated

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
15	0.93	0.643	37779_at	Y08134	Hs.123659	27293	acid sphingomyelinase-like phosphodiesterase
16	0.92	0.641	38773_at	AB003151	Hs.88778	873	carbonyl reductase 1
17	0.9	0.639	700_s_at	HG371-HT26388			Mucin 1, Epithelial, Alt. Splice 9
18	0.89	0.639	37004_at	J02761	Hs.76305	6439	surfactant, pulmonary-associated protein B
19	0.88	0.639	38986_at	Z49835	Hs.289101	2923	glucose regulated protein, 58kD
20	0.88	0.638	40685_at	U10868	Hs.83155	221	aldehyde dehydrogenase 7
21	0.87	0.636	35938_at	M72393	Hs.211587	5321	phospholipase A2, group IVA (cytosolic, calcium-dependent)
22	0.87	0.632	41267_at	AB028972	Hs.227835	22980	KIAA1049 protein
23	0.86	0.628	34839_at	AB029027	Hs.279039	22910	KIAA1104 protein
24	0.85	0.627	38784_g_at	J05581	Hs.89603	4582	mucin 1, transmembrane
25	0.83	0.627	33439_at	D15050	Hs.232068	6935	transcription factor 8 (represses interleukin 2 expression)
26	0.82	0.627	38429_at	U29344	Hs.83190	2194	fatty acid synthase
27	0.82	0.626	39248_at	N74607	Hs.234642	360	aquaporin 3
28	0.8	0.625	1563_s_at	M58286	Hs.159	7132	tumor necrosis factor receptor superfamily, member 1A
29	0.8	0.623	39260_at	U59185	Hs.23590	9122	solute carrier family 16 (monocarboxylic acid transporters), member 4
30	0.79	0.623	38801_at	AI742846	Hs.9006	9218	VAMP (vesicle-associated membrane protein)-associated protein A (33kD)
31	0.79	0.622	37311_at	AF010400			transaldolase 1
32	0.78	0.622	36200_at	X69838	Hs.75196	10919	ankyrin repeat-containing protein

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
33	0.78	0.620	36938_at	U70063	Hs.75811	427	N-acylsphingosine amidohydrolase (acid ceramidase)
34	0.77	0.618	41051_at	X95073	Hs.96247	7257	translin-associated factor X
35	0.77	0.618	32072_at	U40434	Hs.155981	10232	mesothelin
36	0.76	0.618	41402_at	AL080121	Hs.105460	25849	DKFZP564O0823 protein
37	0.76	0.617	39392_at	AJ002190	Hs.12482	8443	glyceronephosphate O-acyltransferase
38	0.75	0.617	1346_at	S72043	Hs.73133	4504	metallothionein 3 (growth inhibitory factor (neurotrophic))
39	0.74	0.617	34798_at	Z35491	Hs.41714	573	BCL2-associated athanogene
40	0.72	0.616	35151_at	AF089814	Hs.25664	10263	tumor suppressor deleted in oral cancer-related 1
41	0.72	0.616	41772_at	M68840	Hs.183109	4128	monoamine oxidase A
42	0.72	0.613	40223_r_at	AI677689	Hs.296406	9701	KIAA0685 gene product
43	0.71	0.612	37399_at	D17793	Hs.78183	8644	aldo-keto reductase family 1, member C3 (3-alpha hydroxysteroid dehydrogenase, type II)
44	0.71	0.611	37748_at	D86985	Hs.79276	9778	KIAA0232 gene product
45	0.7	0.610	39689_at	AI362017	Hs.135084	1471	cystatin C (amyloid angiopathy and cerebral hemorrhage)
46	0.7	0.610	38827_at	AF038451	Hs.91011	10551	anterior gradient 2 (Xenepus laevis) homolog
47	0.7	0.609	36945_at	X94910	Hs.75841	10961	endoplasmic reticulum lumenal protein
48	0.7	0.608	1662_r_at	HG2261-HT2351			Antigen, Prostate Specific, Alt. Splice Form 2
49	0.69	0.608	38482_at	AJ011497	Hs.278562	1366	claudin 7
50	0.68	0.606	33325_at	W26667	Hs.184581		cDNA

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
51	0.68	0.606	35311_at	AF084523	Hs.5710	8804	cellular repressor of E1A-stimulated genes
52	0.67	0.604	38063_at	U00952	Hs.8068	57326	hematopoietic PBX-interacting protein
53	0.67	0.604	33863_at	U65785	Hs.277704	10525	oxygen regulated protein (150kD)
54	0.66	0.604	38790_at	L25879	Hs.89649	2052	epoxide hydrolase 1, microsomal (xenobiotic)
55	0.66	0.602	35214_at	AF061016	Hs.28309	7358	UDP-glucose dehydrogenase
56	0.66	0.602	37279_at	U10550	Hs.79022	2669	GTP-binding protein overexpressed in skeletal muscle
57	0.65	0.602	37639_at	X07732	Hs.823	3249	hepsin (transmembrane protease, serine 1)
58	0.64	0.602	33730_at	AF095448	Hs.194691	9052	retinoic acid induced 3
59	0.64	0.602	37003_at	X62654	Hs.76294	967	CD63 antigen (melanoma 1 antigen)
60	0.64	0.601	36959_at	U49278	Hs.75875	7335	ubiquitin-conjugating enzyme E2 variant 1
61	0.64	0.601	36488_at	AB011542	Hs.5599	1955	EGF-like-domain, multiple 5
62	0.64	0.601	37552_at	U33632	Hs.79351	3775	potassium channel, subfamily K, member 1 (TWIK-1)
63	0.64	0.601	36540_at	AB018260	Hs.62113	23221	KIAA0717 protein
64	0.63	0.600	40031_at	M74542	Hs.575	218	aldehyde dehydrogenase 3
65	0.63	0.599	34485_r_at	M21868	Hs.118249	10564	brefeldin A-inhibited guanine nucleotide-exchange protein 2
66	0.63	0.599	206_at	M84424			cathepsin E
67	0.63	0.599	38376_at	L46590	Hs.82208	37	acyl-Coenzyme A dehydrogenase, very long chain
68	0.63	0.599	36644_at	D29963	Hs.75564	977	CD151 antigen

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
69	0.63	0.599	36963_at	U30255	Hs.75888	5226	phosphogluconate dehydrogenase
70	0.62	0.599	271_s_at	J05036	Hs.1355	1510	cathepsin E
71	0.62	0.599	36647_at	AA526812	Hs.262823	55699	hypothetical protein FLJ10326
72	0.62	0.599	32081_at	AB023166	Hs.15767	11113	citron (rho-interacting, serine/threonine kinase 21)
73	0.62	0.598	691_g_at	J02783	Hs.75655	5034	procollagen-proline, 2-oxoglutarate 4-dioxygenase (proline 4-hydroxylase), beta polypeptide (protein disulfide isomerase; thyroid hormone binding protein p55)
74	0.62	0.598	34835_at	D87442	Hs.4788	23385	nicastrin
75	0.62	0.598	38642_at	Y10183	Hs.10247	214	activated leucocyte cell adhesion molecule
76	0.62	0.598	32892_at	X85106	Hs.301664	6196	ribosomal protein S6 kinase, 90kD, polypeptide 2
77	0.62	0.597	1826_at	M12174	Hs.204354	388	ras homolog gene family, member B
78	0.61	0.597	38816_at	AF095791	Hs.272023	10579	transforming, acidic coiled-coil containing protein 2
79	0.61	0.597	39379_at	AL049397	Hs.12314		clone DKFZp586C1019
80	0.61	0.595	38385_at	S65738	Hs.82306	11034	destrin (actin depolymerizing factor)
81	0.61	0.595	39698_at	U51712	Hs.13775	84525	hypothetical protein SMAP31
82	0.61	0.595	36151_at	U60644	Hs.74573	23646	similar to vaccinia virus HindIII K4L ORF
83	0.61	0.595	32747_at	X05409	Hs.195432	217	aldehyde dehydrogenase 2, mitochondrial
84	0.6	0.594	39512_s_at	AA457029	Hs.342682		clone RP11-127K18

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Table 4: C4 Markers

[00134] According to the invention, preferred markers are markers 1-30, preferably 1-20, and more preferably 1-10. Highly preferred markers are cathepsin H, folate receptor 1 (adult), BENE protein, and cytochrome b-5.

Class C4

	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
1	1.07	0.786	1411_at	D16154			cytochrome P-450c11
2	1.04	0.704	37021_at	X16832	Hs.288181	1512	cathepsin H
3	1.02	0.701	534_s_at	U20391	Hs.73769	2348	folate receptor 1 (adult)
4	0.95	0.655	38394_at	D42047	Hs.82432	23171	KIAA0089 protein
5	0.94	0.653	1460_g_at	M68941	Hs.73826	5775	protein tyrosine phosphatase, non-receptor type 4 (megakaryocyte)
6	0.92	0.650	33331_at	U17077	Hs.185055	7851	BENE protein
7	0.91	0.648	38336_at	AB023230	Hs.96427	23150	KIAA1013 protein
8	0.89	0.647	31883_at	AF025794	Hs.153792	4552	5-methyltetrahydrofolate-homocysteine methyltransferase reductase
9	0.88	0.641	35016_at	M13560			Ia-associated invariant gamma-chain gene
10	0.87	0.635	1629_s_at	HG3187-HT3366			Tyrosine Phosphatase 1, Non-Receptor, Alt. Splice 3
11	0.87	0.632	37512_at	U89281	Hs.11958	8630	oxidative 3 alpha hydroxysteroid dehydrogenase; retinol dehydrogenase; 3-hydroxysteroid epimerase
12	0.86	0.631	38459_g_at	L39945			cytochrome b-5
13	0.86	0.631	36965_at	U13616	Hs.75893	288	ankyrin 3, node of Ranvier (ankyrin G)
14	0.85	0.630	593_s_at	M34353	Hs.1041	6098	v-ros avian UR2 sarcoma virus oncogene homolog 1

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
15	0.85	0.615	821_s_at	U78793			folate receptor 1 (adult)
16	0.84	0.611	130_s_at	X82850	Hs.197764	7080	thyroid transcription factor 1
17	0.83	0.610	33278_at	AC004381	Hs.181345	6296	SA (rat hypertension-associated) homolog
18	0.82	0.608	33967_at	M31525	Hs.342656	3111	major histocompatibility complex, class II, DN alpha
19	0.82	0.605	35792_at	U67963	Hs.6721	11343	lysophospholipase-like
20	0.81	0.599	33584_at	U35146	Hs.158512	8999	cyclin-dependent kinase-like 2 (CDC2-related kinase)
21	0.8	0.598	38785_at	X52228	Hs.89603	4582	mucin 1, transmembrane
22	0.8	0.597	34198_at	U12128	Hs.211595	5783	protein tyrosine phosphatase, non-receptor type 13 (APO-1/CD95 (Fas)-associated phosphatase)
23	0.8	0.595	33249_at	M16801	Hs.1790	4306	nuclear receptor subfamily 3, group C, member 2
24	0.79	0.592	40310_at	AF051152	Hs.63668	7097	toll-like receptor 2
25	0.79	0.587	37189_at	AL023553	Hs.75835	5372	phosphomannomutase 1
26	0.79	0.587	37038_at	X83467	Hs.76781	5825	ATP-binding cassette, sub-family D (ALD), member 3
27	0.77	0.583	37218_at	D64110	Hs.77311	10950	BTG family, member 3
28	0.77	0.582	34823_at	X60708	Hs.44926	1803	dipeptidylpeptidase IV (CD26, adenosine deaminase complexing protein 2)
29	0.77	0.579	715_s_at	D87002	Hs.284380	2678	similar to rat integral membrane glycoprotein POM121
30	0.77	0.578	38984_at	AB007896	Hs.110	9581	putative L-type neutral amino acid transporter

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
31	0.77	0.577	38627_at	M95585	Hs.250692	3131	hepatic leukemia factor
32	0.77	0.576	39419_at	AB011088	Hs.129872	9043	sperm associated antigen 9
33	0.76	0.575	34760_at	D14664	Hs.2441	9936	KIAA0022 gene product
34	0.76	0.572	554_at	U03634	Hs.301946	3928	lymphoid blast crisis oncogene
35	0.76	0.571	34996_at	U75329	Hs.318545	7113	transmembrane protease, serine 2
36	0.75	0.570	35232_f_at	AI056696	Hs.29463	1070	centrin, EF-hand protein, 3 (CDC31 yeast homolog)
37	0.75	0.570	37886_at	AB015332	Hs.96200	26993	neighbor of A-kinase anchoring protein 95
38	0.74	0.570	36252_at	U43030	Hs.25537	1489	cardiotrophin 1
39	0.74	0.569	1709_g_at	U07620	Hs.151051	5602	mitogen-activated protein kinase 10
40	0.73	0.568	35221_at	X91648	Hs.29117	5813	purine-rich element binding protein A
41	0.73	0.568	33933_at	X63187	Hs.2719	10406	epididymis-specific, whey-acidic protein type, four-disulfide core; putative ovarian carcinoma marker
42	0.73	0.567	33561_at	X80031	Hs.530	1285	collagen, type IV, alpha 3 (Goodpasture antigen)
43	0.73	0.566	41809_at	AI656421	Hs.322404	79161	hypothetical protein MGC4175
44	0.73	0.566	36511_at	AB020658	Hs.5867	22908	KIAA0851 protein
45	0.73	0.565	41109_at	M31452	Hs.1012	722	complement component 4-binding protein, alpha
46	0.72	0.562	32893_s_at	M30474	Hs.289098	2679	gamma-glutamyltransferase 2
47	0.72	0.561	39345_at	AI525834	Hs.119529	10577	Niemann-Pick disease, type C2 gene
48	0.72	0.559	39115_at	AL050275	Hs.9383	25982	DKFZP566D213 protein
49	0.72	0.558	40508_at	AF025887	Hs.169907	2941	glutathione S-transferase A4
50	0.71	0.557	1137_at	L20852	Hs.10018	6575	solute carrier family 20 (phosphate transporter), member 2

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
51	0.71	0.557	40101_g_at	U72206	Hs.337774	9181	rho/rac guanine nucleotide exchange factor (GEF) 2
52	0.7	0.556	711_at	HG2339-HT2435			Nuclear Factor 1, Variant Hepatic
53	0.7	0.555	40834_at	AB002298	Hs.173035	23037	KIAA0300 protein
54	0.7	0.554	41302_at	R59606	Hs.4113	10768	S-adenosylhomocysteine hydrolase-like 1
55	0.69	0.552	1922_g_at	HG2510-HT2606			Ras-Specific Guanine Nucleotide-Releasing Factor
56	0.69	0.552	37579_at	L47738	Hs.258503	26999	p53 inducible protein
57	0.69	0.551	32902_at	U28281	Hs.2199	6344	secretin receptor
58	0.69	0.548	704_at	HG4167-HT4437			Nuclear Factor 1, A Type
59	0.69	0.547	37676_at	AF056490	Hs.78746	5151	phosphodiesterase 8A
60	0.69	0.547	33621_at	X71348			transcription factor 2, hepatic; LF-B3; variant hepatic nuclear factor
61	0.69	0.547	38252_s_at	U84007	Hs.904	178	amylo-1,6-glucosidase, 4-alpha-glucanotransferase (glycogen debranching enzyme, glycogen storage disease type III)
62	0.68	0.544	34213_at	AB020676	Hs.21543	23286	KIAA0869 protein
63	0.68	0.544	37405_at	U29091	Hs.334841	8991	selenium binding protein 1
64	0.68	0.543	34767_at	AI670788	Hs.24719	64112	modulator of apoptosis 1
65	0.68	0.542	35955_at	S80864	Hs.262219	25835	cytochrome c-like antigen
66	0.68	0.541	38790_at	L25879	Hs.89649	2052	epoxide hydrolase 1, microsomal (xenobiotic)
67	0.68	0.540	36508_at	AF030186	Hs.58367	2239	glypican 4
68	0.68	0.540	33942_s_at	AF004563	Hs.239356	6812	syntaxin binding protein 1
69	0.67	0.540	37629_at	M55268	Hs.82201	1459	casein kinase 2, alpha prime polypeptide

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
70	0.67	0.539	32822_at	J02966	Hs.2043	291	solute carrier family 25 (mitochondrial carrier; adenine nucleotide translocator), member 4
71	0.67	0.538	35472_at	Y10745	Hs.17287	3772	potassium inwardly-rectifying channel, subfamily J, member 15
72	0.67	0.537	34163_g_at	D84111	Hs.80248	11030	RNA-binding protein gene with multiple splicing
73	0.67	0.536	31925_s_at	L26584	Hs.169350	5923	Ras protein-specific guanine nucleotide-releasing factor 1
74	0.67	0.536	32854_at	AB014596	Hs.21229	23291	f-box and WD-40 domain protein 1B
75	0.67	0.535	35645_at	AL050148	Hs.31834		clone DKFZp586G1520
76	0.66	0.535	1986_at	X74594	Hs.79362	5934	retinoblastoma-like 2 (p130)
77	0.66	0.533	1938_at	K03218			v-src avian sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog
78	0.66	0.532	1616_at	D14838	Hs.111	2254	fibroblast growth factor 9 (glia-activating factor)
79	0.66	0.532	41440_at	D82061	Hs.288354	7923	FabG (beta-ketoacyl-[acyl-carrier-protein] reductase, E coli) like
80	0.66	0.530	41129_at	D26067	Hs.174905	23027	KIAA0033 protein
81	0.66	0.530	40209_at	U72671	Hs.151250	7087	intercellular adhesion molecule 5, telencephalin
82	0.65	0.529	32676_at	M93405	Hs.293970	4329	methylmalonate-semialdehyde dehydrogenase
83	0.65	0.528	36557_at	M92303	Hs.635	782	calcium channel, voltage-dependent, beta 1 subunit
84	0.65	0.528	35228_at	Y08682	Hs.29331	1375	carnitine palmitoyltransferase I, muscle

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
85	0.65	0.527	1667_s_at	J02871	Hs.687	1580	cytochrome P450, subfamily IVB, polypeptide 1
86	0.65	0.526	40701_at	U75362	Hs.85482	8975	ubiquitin specific protease 13 (isopeptidase T-3)
87	0.65	0.525	40343_at	AJ005814	Hs.70954	3204	homeo box A7
88	0.65	0.524	39301_at	X85030	Hs.40300	825	calpain 3, (p94)
89	0.65	0.524	35435_s_at	AF001903	Hs.8110	3033	L-3-hydroxyacyl-Coenzyme A dehydrogenase, short chain
90	0.64	0.523	34235_at	AB018301	Hs.22039	23282	KIAA0758 protein
91	0.64	0.523	37344_at	X62744	Hs.77522	3108	major histocompatibility complex, class II, DM alpha
92	0.64	0.522	41120_at	D14686			aminomethyltransferase (glycine cleavage system protein T)
93	0.64	0.522	40673_at	U12778	Hs.81934	36	acyl-Coenzyme A dehydrogenase, short/branched chain
94	0.63	0.521	34353_at	AB014548	Hs.31921	23244	KIAA0648 protein
95	0.63	0.520	35285_at	AF007216	Hs.5462	8671	solute carrier family 4, sodium bicarbonate cotransporter, member 4
96	0.63	0.520	40822_at	L41067	Hs.172674	4775	nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 3
97	0.63	0.519	41331_at	R93981	Hs.24279	9860	KIAA0806 gene product
98	0.63	0.519	40278_at	AB029003	Hs.155546	23062	KIAA1080 protein; Golgi-associated, gamma-adaptin ear containing, ARF-binding protein 2
99	0.63	0.519	36828_at	AB002324	Hs.301094	23361	KIAA0326 protein
100	0.63	0.519	40128_at	D79993	Hs.132853	9685	KIAA0171 gene product
101	0.63	0.519	35382_at	AF043244	Hs.278439	8996	nucleolar protein 3 (apoptosis repressor with CARD domain)

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
102	0.63	0.518	40217_s_at	U65887	Hs.152981	1040	CDP-diacylglycerol synthase (phosphatidate cytidylyltransferase) 1
103	0.63	0.518	38095_i_at	M83664	Hs.814	3115	major histocompatibility complex, class II, DP beta 1
104	0.62	0.518	34555_at	X63755	Hs.2743	3846	keratin, cuticle, ultrahigh sulphur 1
105	0.62	0.517	33263_at	X67098			rTS beta protein
106	0.62	0.517	33267_at	AF035315	Hs.180737		clone 23664 and 23905
107	0.62	0.517	1594_at	J05448	Hs.79402	5432	polymerase (RNA) II (DNA directed) polypeptide C (33kD)
108	0.62	0.516	40013_at	Y12696	Hs.54570	1193	chloride intracellular channel 2
109	0.62	0.516	32122_at	L31573	Hs.16340	6821	sulfite oxidase
110	0.62	0.515	34800_at	AL039458	Hs.4193	26018	ortholog of mouse integral membrane glycoprotein LIG-1
111	0.62	0.515	41723_s_at	M32578	Hs.180255	3123	major histocompatibility complex, class II, DR beta 1
112	0.62	0.515	38683_s_at	AB029008	Hs.301226	57450	KIAA1085 protein
113	0.62	0.514	32235_at	AB011116	Hs.284251	23295	KIAA0544 protein
114	0.62	0.514	41689_at	R16035	Hs.12701	51090	plasmolipin
115	0.62	0.514	38318_at	AL050128	Hs.95260	51439	Autosomal Highly Conserved Protein
116	0.61	0.513	1619_g_at	D21241			cytochrome P-450 aromatase
117	0.61	0.513	39266_at	AF070632	Hs.23729		clone 24405
118	0.61	0.513	40711_at	AL049340	Hs.86405		clone DKFZp564P056
119	0.61	0.512	39247_at	U66689	Hs.274260	368	ATP-binding cassette, sub-family C (CFTR/MRP), member 6
120	0.61	0.512	39820_at	AF001549	Hs.110103	54700	RNA polymerase I transcription factor RRN3

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
121	0.61	0.511	39974_at	AF039917	Hs.47042	956	ectonucleoside triphosphate diphosphohydrolase 3
122	0.61	0.511	37704_at	Z14093	Hs.78950	593	branched chain keto acid dehydrogenase E1, alpha polypeptide (maple syrup urine disease)
123	0.61	0.510	34521_at	AB001872	Hs.21291	9175	mitogen-activated protein kinase kinase kinase 13
124	0.6	0.509	38072_at	AL031432	Hs.8084	57035	hypothetical protein dJ465N24.2.1
125	0.6	0.509	40149_at	AL049924	Hs.15744	25970	SH2-B homolog
126	0.6	0.509	39138_g_at	X80878	Hs.95262	4798	nuclear factor related to kappa B binding protein
127	0.6	0.508	38064_at	X79882	Hs.80680	9961	major vault protein
128	0.6	0.508	34473_at	AF051151	Hs.114408	7100	toll-like receptor 5
129	0.6	0.508	36755_s_at	M75914	Hs.68876	3568	interleukin 5 receptor, alpha
130	0.6	0.507	41686_s_at	AL042668	Hs.337629		cDNA, 5 end
131	0.6	0.507	41424_at	L48516	Hs.296259	5446	paraoxonase 3
132	0.6	0.507	903_at	L42373	Hs.155079	5525	protein phosphatase 2, regulatory subunit B (B56), alpha isoform
133	0.6	0.506	35408_i_at	X16281	Hs.278480	7595	zinc finger protein 44 (KOX 7)
134	0.59	0.506	1270_at	M64788	Hs.75151	5909	RAP1, GTPase activating protein 1
135	0.59	0.506	1087_at	M60459	Hs.89548	2057	erythropoietin receptor
136	0.59	0.505	33290_at	M74161	Hs.182577	3633	inositol polyphosphate-5-phosphatase, 75kD
137	0.59	0.505	39408_at	Z80345	Hs.127610	35	acyl-Coenzyme A dehydrogenase, C-2 to C-3 short chain
138	0.59	0.505	40766_at	U24578	Hs.278625	721	complement component 4B
139	0.59	0.505	39612_at	AL050061	Hs.27371		clone DKFZp566J123
140	0.59	0.504	38850_at	M11119	Hs.272951		endogenous retrovirus envelope region mRNA (PL1)
141	0.59	0.504	34529_at	W26760	Hs.336635		cDNA

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
142	0.59	0.504	40394_at	L17128	Hs.77719	2677	gamma-glutamyl carboxylase
143	0.59	0.503	37811_at	AF042792	Hs.127436	9254	calcium channel, voltage-dependent, alpha 2/delta subunit 2
144	0.58	0.503	37150_at	AB026190	Hs.106290	27252	Kelch motif containing protein
145	0.58	0.503	41346_at	AJ007583	Hs.25220	9215	like-glycosyltransferase
146	0.58	0.502	37609_at	U01833	Hs.81469	4682	nucleotide binding protein 1 (E.coli MinD like)
147	0.58	0.502	35988_i_at	AI417075	Hs.42343	84148	hypothetical protein FLJ14040
148	0.58	0.501	32427_at	U66583	Hs.72911	1421	crystallin, gamma D
149	0.58	0.501	37151_at	AF052120	Hs.106334		clone 23836
150	0.58	0.501	37172_at	M75106	Hs.75572	1361	carboxypeptidase B2 (plasma)
151	0.58	0.500	35815_at	AL049470	Hs.306184	25767	Huntingtin interacting protein B
152	0.58	0.499	37722_s_at	U26266	Hs.79064	1725	deoxyhypusine synthase
153	0.58	0.499	40600_at	AW024467	Hs.172847	3338	DnaJ (Hsp40) homolog, subfamily C, member 4
154	0.57	0.499	38086_at	AB007935	Hs.81234	3321	immunoglobulin superfamily, member 3
155	0.57	0.499	38285_at	AF039397			crystallin, mu
156	0.57	0.499	41381_at	AB002306	Hs.10351	23337	KIAA0308 protein
157	0.57	0.498	34716_at	AF067730	Hs.3530	63902	TLS-associated serine-arginine protein 2
158	0.57	0.498	38492_at	D55639	Hs.169139	8942	kynureninase (L-kynurenine hydrolase)
159	0.57	0.497	39438_at	AF039081	Hs.13313	1389	cAMP responsive element binding protein-like 2
160	0.57	0.497	36997_at	J04809	Hs.76240	203	adenylate kinase 1
161	0.57	0.497	32076_at	D83407	Hs.156007	10231	Down syndrome critical region gene 1-like 1
162	0.57	0.497	32185_at	U00946	Hs.184592	65125	protein kinase, lysine deficient 1

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
163	0.57	0.496	36538_at	AB018314	Hs.6162	23368	KIAA0771 protein
164	0.56	0.496	41339_at	AF043117	Hs.24594	10277	ubiquitination factor E4B (homologous to yeast UFD2)
165	0.56	0.495	32144_at	AL050135	Hs.166891	5993	regulatory factor X, 5 (influences HLA class II expression)
166	0.56	0.495	37402_at	D26129	Hs.78224	6035	ribonuclease, RNase A family, 1 (pancreatic)
167	0.56	0.494	700_s_at	HG371-HT26388			Mucin 1, Epithelial, Alt. Splice 9
168	0.56	0.494	33521_at	M63962	Hs.36992	495	ATPase, H+/K+ exchanging, alpha polypeptide
169	0.56	0.494	34934_at	L29376	Hs.132807		(clone 3.8-1) MHC class I
170	0.56	0.494	41018_at	AL050015	Hs.92700	25864	DKFZP564O243 protein
171	0.56	0.493	37539_at	AB023176	Hs.79219	23179	RalGDS-like gene; KIAA0959 protein
172	0.56	0.493	36626_at	X87176	Hs.75441	3295	hydroxysteroid (17-beta) dehydrogenase 4
173	0.56	0.493	36012_at	Y09631	Hs.43913	10464	PIBF1 gene product
174	0.56	0.493	41491_s_at	AB028944	Hs.29189	23250	ATPase, Class VI, type 11A
175	0.56	0.493	32746_at	AF015451	Hs.195175	8837	CASP8 and FADD-like apoptosis regulator
176	0.56	0.492	40833_r_at	AL050126	Hs.234265	26092	DKFZP586G011 protein
177	0.56	0.492	34256_at	AB018356	Hs.225939	8869	sialyltransferase 9 (CMP-NeuAc:lactosylceramide alpha-2,3-sialyltransferase; GM3 synthase)

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
178	0.56	0.491	AFFX-DapX-M_at	L38424			B subtilis dapB, jojF, jojG genes corresponding to nucleotides 1358-3197 of L38424 (-5, -M, -3 represent transcript regions 5 prime, Middle, and 3 prime respectively)
179	0.55	0.491	40547_at	AI688516	Hs.163867	4695	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 2 (8kD, B8)
180	0.55	0.491	41488_at	AC002394	Hs.144852		hypothetical protein A-211C6.1
181	0.55	0.491	41501_at	AF004849	Hs.30148	10114	homeodomain-interacting protein kinase 3
182	0.55	0.490	35287_at	AF046888	Hs.54673	8741	tumor necrosis factor (ligand) superfamily, member 13
183	0.55	0.490	33284_at	M19507	Hs.1817	4353	myeloperoxidase
184	0.55	0.490	40152_r_at	Z48054	Hs.158084	5830	peroxisome receptor 1
185	0.55	0.490	34001_at	AF033199	Hs.8198	7754	zinc finger protein 204
186	0.55	0.489	1527_s_at	U50527	Hs.22174		BRCA2 region
187	0.55	0.489	34141_at	AL109681	Hs.226017		clone EUROIMAGE 112333
188	0.55	0.489	34116_at	AF038852	Hs.21903	785	calcium channel, voltage-dependent, beta 4 subunit
189	0.55	0.488	36806_at	X83877	Hs.289104	11256	Alu-binding protein with zinc finger domain
190	0.55	0.488	39557_at	AI625844	Hs.295963		cDNA, 3 end
191	0.55	0.487	40595_at	AI345337	Hs.301266	6949	Treacher Collins-Franceschetti syndrome 1
192	0.55	0.487	39993_at	D11466	Hs.51	5277	phosphatidylinositol glycan, class A (paroxysmal nocturnal hemoglobinuria)
193	0.55	0.487	39947_at	AJ006352	Hs.42331	1945	ephrin-A4

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
194	0.55	0.487	785_at	U96114	Hs.315493	11060	Nedd-4-like ubiquitin-protein ligase
195	0.55	0.487	33569_at	D50532	Hs.54403	10462	macrophage lectin 2 (calcium dependent)
196	0.54	0.486	39171_at	W21787	Hs.99816	56998	beta-catenin-interacting protein ICAT
197	0.54	0.486	39678_at	D10511			acetyl-Coenzyme A acetyltransferase 1 (acetoacetyl Coenzyme A thiolase)
198	0.54	0.486	881_at	M35198	Hs.123125	3694	integrin, beta 6
199	0.54	0.485	40064_at	AB011121	Hs.154248	66008	amyotrophic lateral sclerosis 2 (juvenile) chromosome region, candidate 3
200	0.54	0.485	33800_at	AF036927	Hs.20196	115	adenylate cyclase 9

Table 5: Normal Lung Markers

[00135] According to the invention, preferred markers are markers 1-30, preferably 1-20, and more preferably 1-10. Highly preferred markers are transforming growth factor beta receptor II, dihydropyrimidinase-like 2, and tetranectin.

Class Norm

	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
1	1.97	0.677	32542_at	AF063002	Hs.239069	2273	four and a half LIM domains 1
2	1.85	0.631	1815_g_at	D50683	Hs.82028	7048	transforming growth factor, beta receptor II (70-80kD)
3	1.82	0.626	36119_at	AF070648	Hs.74034		clone 24651
4	1.75	0.603	35868_at	M91211	Hs.184	177	advanced glycosylation end product-specific receptor
5	1.71	0.600	39031_at	AA152406	Hs.114346	1346	cytochrome c oxidase subunit VIIa polypeptide 1 (muscle)

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
6	1.7	0.594	37398_at	AA100961	Hs.78146	5175	platelet/endothelial cell adhesion molecule (CD31 antigen)
7	1.7	0.592	40331_at	AF035819	Hs.67726	8685	macrophage receptor with collagenous structure
8	1.7	0.589	40607_at	U97105	Hs.173381	1808	dihydropyrimidinase-like 2
9	1.7	0.588	40841_at	AF049910	Hs.173159	6867	transforming, acidic coiled-coil containing protein 1
10	1.69	0.587	38454_g_at	X15606	Hs.83733	3384	intercellular adhesion molecule 2
11	1.65	0.582	36569_at	X64559	Hs.65424	7123	tetranectin (plasminogen-binding protein)
12	1.63	0.578	39066_at	L38486	Hs.296049	4239	microfibrillar-associated protein 4
13	1.6	0.576	40282_s_at	M84526	Hs.155597	1675	D component of complement (adipsin)
14	1.6	0.575	34320_at	AL050224	Hs.29759	22939	polymerase I and transcript release factor
15	1.6	0.574	37027_at	M80899	Hs.301417	195	AHNAK nucleoprotein (desmoyokin)
16	1.58	0.574	33328_at	W28612	Hs.296326		cDNA
17	1.58	0.573	35985_at	AB023137	Hs.42322	11217	A kinase (PRKA) anchor protein 2
18	1.57	0.572	770_at	D00632	Hs.336920	2878	glutathione peroxidase 3 (plasma)
19	1.55	0.570	38177_at	AJ001015	Hs.155106	10266	receptor (calcitonin) activity modifying protein 2
20	1.54	0.568	39760_at	AL031781	Hs.15020	9444	homolog of mouse quaking QKI (KH domain RNA binding protein)
21	1.54	0.567	268_at	L34657			platelet/endothelial cell adhesion molecule (CD31 antigen)
22	1.53	0.567	33756_at	U39447	Hs.198241	8639	amine oxidase, copper containing 3 (vascular adhesion protein 1)

BNSDOCID: <WO_____03029273A2_I_>

	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
23	1.51	0.567	32562_at	X72012	Hs.76753	2022	endoglin (Osler-Rendu-Weber syndrome 1)
24	1.51	0.566	40419_at	X85116	Hs.160483	2040	erythrocyte membrane protein band 7.2 (stomatin)
25	1.48	0.565	40994_at	L15388	Hs.211569	2869	G protein-coupled receptor kinase 5
26	1.48	0.564	38430_at	AA128249	Hs.83213	2167	fatty acid binding protein 4, adipocyte
27	1.47	0.564	36155_at	D87465	Hs.74583	9806	KIAA0275 gene product
28	1.47	0.564	39631_at	U52100	Hs.29191	2013	epithelial membrane protein 2
29	1.45	0.563	36627_at	X86693	Hs.75445	8404	SPARC-like 1 (mast9, hevin)
30	1.45	0.562	35730_at	X03350	Hs.4	125	alcohol dehydrogenase 2 (class I), beta polypeptide
31	1.42	0.561	34708_at	D88587	Hs.333383	8547	ficolin (collagen/fibrinogen domain-containing) 3 (Hakata antigen)
32	1.42	0.560	39775_at	X54486	Hs.151242	710	serine (or cysteine) proteinase inhibitor, clade G (C1 inhibitor), member 1
33	1.41	0.560	38239_at	AI312905	Hs.16762		cDNA, 3 end
34	1.41	0.559	35261_at	W07033	Hs.5210	9535	glia maturation factor, gamma
35	1.4	0.559	39350_at	U50410	Hs.119651	2719	glypican 3
36	1.39	0.559	40560_at	U28049	Hs.168357	6909	T-box 2
37	1.39	0.559	607_s_at	M10321	Hs.110802	7450	von Willebrand factor
38	1.36	0.557	1596_g_at	L06139	Hs.89640	7010	TEK tyrosine kinase, endothelial (venous malformations, multiple cutaneous and mucosal)
39	1.36	0.557	38653_at	D11428	Hs.103724	5376	peripheral myelin protein 22
40	1.35	0.557	36577_at	Z24725	Hs.75260	10979	mitogen inducible 2
41	1.33	0.555	37976_at	AL034397	Hs.8904	11326	Ig superfamily protein
42	1.33	0.554	34210_at	N90866	Hs.276770	1043	CDW52 antigen (CAMPATH-1 antigen)
43	1.33	0.554	38508_s_at	U89337	Hs.169886	7148	DIR1 protein

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
44	1.32	0.553	32780_at	AB018271	Hs.198689	26029	KIAA0728 protein
45	1.31	0.553	39634_at	AB017168	Hs.29802	9353	slit (Drosophila) homolog 2
46	1.31	0.552	38995_at	AF000959	Hs.110903	7122	claudin 5 (transmembrane protein deleted in velocardiofacial syndrome)
47	1.3	0.552	37099_at	AI806222	Hs.100194	241	arachidonate 5-lipoxygenase-activating protein
48	1.3	0.552	37196_at	X79981	Hs.76206	1003	cadherin 5, type 2, VE-cadherin (vascular epithelium)
49	1.29	0.552	36958_at	X95735	Hs.75873	7791	zyxin
50	1.28	0.552	38685_at	AL035306	Hs.106823	84295	hypothetical protein MGC14797
51	1.28	0.551	37307_at	X04828	Hs.77269	2771	guanine nucleotide binding protein (G protein), alpha inhibiting activity polypeptide 2
52	1.27	0.551	38704_at	AB007934	Hs.108258	23499	actin binding protein; macrophin (microfilament and actin filament cross-linker protein)
53	1.27	0.551	32166_at	AB028950	Hs.18420	7094	KIAA1027 protein
54	1.26	0.550	34874_at	AJ004832	Hs.5038	10908	neuropathy target esterase
55	1.26	0.549	36937_s_at	U90878	Hs.75807	9124	PDZ and LIM domain 1 (elfin)
56	1.25	0.549	37247_at	AF047419	Hs.78061	6943	transcription factor 21
57	1.25	0.549	39541_at	W52003	Hs.10491	57493	KIAA1237 protein
58	1.25	0.547	590_at	M32334			intercellular adhesion molecule 2
59	1.24	0.547	37168_at	AB013924	Hs.10887	27074	similar to lysosome-associated membrane glycoprotein
60	1.23	0.547	39038_at	AF093118	Hs.11494	10516	fibulin 5
61	1.23	0.547	40456_at	AL049963	Hs.284205	64116	up-regulated by BCG-CWS
62	1.23	0.546	40202_at	D31716	Hs.150557	687	basic transcription element binding protein 1

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
63	1.21	0.546	31856_at	Z24680	Hs.151641	2615	glycoprotein A repetitions predominant
64	1.2	0.545	32321_at	X56841	Hs.181392	3133	major histocompatibility complex, class I, E
65	1.19	0.545	37042_at	U09577	Hs.76873	8692	hyaluronoglucosaminidase 2
66	1.19	0.545	1897_at	L07594	Hs.79059	7049	transforming growth factor, beta receptor III (betaglycan, 300kD)
67	1.18	0.544	35783_at	H93123	Hs.66708	9341	vesicle-associated membrane protein 3 (cellubrevin)
68	1.17	0.544	32052_at	L48215	Hs.155376	3043	hemoglobin, beta
69	1.17	0.544	33862_at	AF017786	Hs.173717	8613	phosphatidic acid phosphatase type 2B
70	1.16	0.543	32812_at	AB029025	Hs.202949	22998	KIAA1102 protein
71	1.16	0.543	36452_at	AB028952	Hs.5307	11346	synaptopodin
72	1.15	0.542	37407_s_at	AF013570	Hs.78344	4629	myosin, heavy polypeptide 11, smooth muscle
73	1.15	0.541	38406_f_at	AI207842	Hs.8272	5730	prostaglandin D2 synthase (21kD, brain)
74	1.14	0.541	216_at	M98539			prostaglandin D2 synthase (21kD, brain)
75	1.14	0.541	38700_at	M33146	Hs.108080	1465	cysteine and glycine-rich protein 1
76	1.13	0.541	39182_at	U87947	Hs.9999	2014	epithelial membrane protein 3
77	1.13	0.541	39315_at	D13628	Hs.2463	284	angiopoietin 1
78	1.13	0.540	36207_at	D67029	Hs.75232	6397	SEC14 (S. cerevisiae)-like 1
79	1.13	0.540	38338_at	AI201108	Hs.9651	6237	related RAS viral (r-ras) oncogene homolog
80	1.11	0.540	38691_s_at	J03553	Hs.1074	6440	surfactant, pulmonary-associated protein C
81	1.11	0.539	32109_at	AA524547	Hs.160318	5348	FXYD domain-containing ion transport regulator 1 (phospholemman)
82	1.11	0.539	38044_at	AF035283	Hs.8022	11170	TU3A protein
83	1.1	0.537	40567_at	X01703	Hs.272897	7846	Tubulin, alpha, brain-specific

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
84	1.1	0.537	36908_at	M93221			mannose receptor, C type 1
85	1.1	0.537	35183_at	U78735	Hs.26630	21	ATP-binding cassette, sub-family A (ABC1), member 3
86	1.09	0.537	538_at	S53911	Hs.85289	947	CD34 antigen
87	1.09	0.536	33283_at	AF106941	Hs.18142	409	arrestin, beta 2
88	1.08	0.536	33295_at	X85785	Hs.183	2532	Duffy blood group
89	1.08	0.536	38972_at	AF052169	Hs.109438		clone 24775
90	1.07	0.536	33137_at	Y13622	Hs.85087	8425	latent transforming growth factor beta binding protein 4
91	1.07	0.535	39588_at	AF055872	Hs.26401	8742	tumor necrosis factor (ligand) superfamily, member 12
92	1.06	0.535	38786_at	AL079279	Hs.8963		clone EUROIMAGE 248114
93	1.06	0.535	33833_at	J05243	Hs.77196	6709	spectrin, alpha, non-erythrocytic 1 (alpha-fodrin)
94	1.06	0.534	35164_at	AF084481	Hs.26077	7466	Wolfram syndrome 1 (wolframin)
95	1.05	0.534	37718_at	D43636	Hs.79025	23182	KIAA0096 protein
96	1.05	0.534	1780_at	M19722	Hs.1422	2268	Gardner-Rasheed feline sarcoma viral (v-fgr) oncogene homolog
97	1.05	0.534	36668_at	M28713			diaphorase (NADH) (cytochrome b-5 reductase)
98	1.05	0.534	41338_at	AI951946	Hs.21907	11143	histone acetyltransferase
99	1.04	0.533	32527_at	AI381790	Hs.74120	10974	adipose specific 2
100	1.04	0.533	34363_at	Z11793	Hs.3314	6414	selenoprotein P, plasma, 1
101	1.04	0.533	37743_at	U60060	Hs.79226	9638	fasciculation and elongation protein zeta 1 (zygin I)
102	1.03	0.533	32838_at	S67247	Hs.296842		smooth muscle myosin heavy chain isoform SMemb [human, umbilical cord, fetal aorta,
103	1.03	0.533	40739_at	M83670	Hs.89485	762	carbonic anhydrase IV
104	1.03	0.533	39057_at	L04733	Hs.117977	3831	kinesin 2 (60-70kD)
105	1.03	0.532	35625_at	X94630	Hs.3107	976	CD97 antigen

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
23	1.51	0.567	32562_at	X72012	Hs.76753	2022	endoglin (Osler-Rendu-Weber syndrome 1)
24	1.51	0.566	40419_at	X85116	Hs.160483	2040	erythrocyte membrane protein band 7.2 (stomatin)
25	1.48	0.565	40994_at	L15388	Hs.211569	2869	G protein-coupled receptor kinase 5
26	1.48	0.564	38430_at	AA128249	Hs.83213	2167	fatty acid binding protein 4, adipocyte
27	1.47	0.564	36155_at	D87465	Hs.74583	9806	KIAA0275 gene product
28	1.47	0.564	39631_at	U52100	Hs.29191	2013	epithelial membrane protein 2
29	1.45	0.563	36627_at	X86693	Hs.75445	8404	SPARC-like 1 (mast9, hevin)
30	1.45	0.562	35730_at	X03350	Hs.4	125	alcohol dehydrogenase 2 (class I), beta polypeptide
31	1.42	0.561	34708_at	D88587	Hs.333383	8547	ficolin (collagen/fibrinogen domain-containing) 3 (Hakata antigen)
32	1.42	0.560	39775_at	X54486	Hs.151242	710	serine (or cysteine) proteinase inhibitor, clade G (C1 inhibitor), member 1
33	1.41	0.560	38239_at	AI312905	Hs.16762		cDNA, 3 end
34	1.41	0.559	35261_at	W07033	Hs.5210	9535	glia maturation factor, gamma
35	1.4	0.559	39350_at	U50410	Hs.119651	2719	glypican 3
36	1.39	0.559	40560_at	U28049	Hs.168357	6909	T-box 2
37	1.39	0.559	607_s_at	M10321	Hs.110802	7450	von Willebrand factor
38	1.36	0.557	1596_g_at	L06139	Hs.89640	7010	TEK tyrosine kinase, endothelial (venous malformations, multiple cutaneous and mucosal)
39	1.36	0.557	38653_at	D11428	Hs.103724	5376	peripheral myelin protein 22
40	1.35	0.557	36577_at	Z24725	Hs.75260	10979	mitogen inducible 2
41	1.33	0.555	37976_at	AL034397	Hs.8904	11326	Ig superfamily protein
42	1.33	0.554	34210_at	N90866	Hs.276770	1043	CDW52 antigen (CAMPATH-1 antigen)
43	1.33	0.554	38508_s_at	U89337	Hs.169886	7148	DIR1 protein

BNSDOCID: <WO_____03029273A2_I_>

	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
44	1.32	0.553	32780_at	AB018271	Hs.198689	26029	KIAA0728 protein
45	1.31	0.553	39634_at	AB017168	Hs.29802	9353	slit (Drosophila) homolog 2
46	1.31	0.552	38995_at	AF000959	Hs.110903	7122	claudin 5 (transmembrane protein deleted in velocardiofacial syndrome)
47	1.3	0.552	37099_at	AI806222	Hs.100194	241	arachidonate 5-lipoxygenase-activating protein
48	1.3	0.552	37196_at	X79981	Hs.76206	1003	cadherin 5, type 2, VE-cadherin (vascular epithelium)
49	1.29	0.552	36958_at	X95735	Hs.75873	7791	zyxin
50	1.28	0.552	38685_at	AL035306	Hs.106823	84295	hypothetical protein MGC14797
51	1.28	0.551	37307_at	X04828	Hs.77269	2771	guanine nucleotide binding protein (G protein), alpha inhibiting activity polypeptide 2
52	1.27	0.551	38704_at	AB007934	Hs.108258	23499	actin binding protein; macrophin (microfilament and actin filament cross-linker protein)
53	1.27	0.551	32166_at	AB028950	Hs.18420	7094	KIAA1027 protein
54	1.26	0.550	34874_at	AJ004832	Hs.5038	10908	neuropathy target esterase
55	1.26	0.549	36937_s_at	U90878	Hs.75807	9124	PDZ and LIM domain 1 (elfin)
56	1.25	0.549	37247_at	AF047419	Hs.78061	6943	transcription factor 21
57	1.25	0.549	39541_at	W52003	Hs.10491	57493	KIAA1237 protein
58	1.25	0.547	590_at	M32334			intercellular adhesion molecule 2
59	1.24	0.547	37168_at	AB013924	Hs.10887	27074	similar to lysosome-associated membrane glycoprotein
60	1.23	0.547	39038_at	AF093118	Hs.11494	10516	fibulin 5
61	1.23	0.547	40456_at	AL049963	Hs.284205	64116	up-regulated by BCG-CWS
62	1.23	0.546	40202_at	D31716	Hs.150557	687	basic transcription element binding protein 1

BNSDOCID: <WO_____03029273A2_I_>

	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
63	1.21	0.546	31856_at	Z24680	Hs.151641	2615	glycoprotein A repetitions predominant
64	1.2	0.545	32321_at	X56841	Hs.181392	3133	major histocompatibility complex, class I, E
65	1.19	0.545	37042_at	U09577	Hs.76873	8692	hyaluronoglucosaminidase 2
66	1.19	0.545	1897_at	L07594	Hs.79059	7049	transforming growth factor, beta receptor III (betaglycan, 300kD)
67	1.18	0.544	35783_at	H93123	Hs.66708	9341	vesicle-associated membrane protein 3 (cellubrevin)
68	1.17	0.544	32052_at	L48215	Hs.155376	3043	hemoglobin, beta
69	1.17	0.544	33862_at	AF017786	Hs.173717	8613	phosphatidic acid phosphatase type 2B
70	1.16	0.543	32812_at	AB029025	Hs.202949	22998	KIAA1102 protein
71	1.16	0.543	36452_at	AB028952	Hs.5307	11346	synaptopodin
72	1.15	0.542	37407_s_at	AF013570	Hs.78344	4629	myosin, heavy polypeptide 11, smooth muscle
73	1.15	0.541	38406_f_at	AI207842	Hs.8272	5730	prostaglandin D2 synthase (21kD, brain)
74	1.14	0.541	216_at	M98539			prostaglandin D2 synthase (21kD, brain)
75	1.14	0.541	38700_at	M33146	Hs.108080	1465	cysteine and glycine-rich protein 1
76	1.13	0.541	39182_at	U87947	Hs.9999	2014	epithelial membrane protein 3
77	1.13	0.541	39315_at	D13628	Hs.2463	284	angiopoietin 1
78	1.13	0.540	36207_at	D67029	Hs.75232	6397	SEC14 (S. cerevisiae)-like 1
79	1.13	0.540	38338_at	AI201108	Hs.9651	6237	related RAS viral (r-ras) oncogene homolog
80	1.11	0.540	38691_s_at	J03553	Hs.1074	6440	surfactant, pulmonary-associated protein C
81	1.11	0.539	32109_at	AA524547	Hs.160318	5348	FXYD domain-containing ion transport regulator 1 (phospholemman)
82	1.11	0.539	38044_at	AF035283	Hs.8022	11170	TU3A protein
83	1.1	0.537	40567_at	X01703	Hs.272897	7846	Tubulin, alpha, brain-specific

BNSDOCID: <WO_____03029273A2_I_>

	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
84	1.1	0.537	36908_at	M93221			mannose receptor, C type 1
85	1.1	0.537	35183_at	U78735	Hs.26630	21	ATP-binding cassette, sub-family A (ABC1), member 3
86	1.09	0.537	538_at	S53911	Hs.85289	947	CD34 antigen
87	1.09	0.536	33283_at	AF106941	Hs.18142	409	arrestin, beta 2
88	1.08	0.536	33295_at	X85785	Hs.183	2532	Duffy blood group
89	1.08	0.536	38972_at	AF052169	Hs.109438		clone 24775
90	1.07	0.536	33137_at	Y13622	Hs.85087	8425	latent transforming growth factor beta binding protein 4
91	1.07	0.535	39588_at	AF055872	Hs.26401	8742	tumor necrosis factor (ligand) superfamily, member 12
92	1.06	0.535	38786_at	AL079279	Hs.8963		clone EUROIMAGE 248114
93	1.06	0.535	33833_at	J05243	Hs.77196	6709	spectrin, alpha, non-erythrocytic 1 (alpha-fodrin)
94	1.06	0.534	35164_at	AF084481	Hs.26077	7466	Wolfram syndrome 1 (wolframin)
95	1.05	0.534	37718_at	D43636	Hs.79025	23182	KIAA0096 protein
96	1.05	0.534	1780_at	M19722	Hs.1422	2268	Gardner-Rasheed feline sarcoma viral (v-fgr) oncogene homolog
97	1.05	0.534	36668_at	M28713			diaphorase (NADH) (cytochrome b-5 reductase)
98	1.05	0.534	41338_at	AI951946	Hs.21907	11143	histone acetyltransferase
99	1.04	0.533	32527_at	AI381790	Hs.74120	10974	adipose specific 2
100	1.04	0.533	34363_at	Z11793	Hs.3314	6414	selenoprotein P, plasma, 1
101	1.04	0.533	37743_at	U60060	Hs.79226	9638	fasciculation and elongation protein zeta 1 (zygin I)
102	1.03	0.533	32838_at	S67247	Hs.296842		smooth muscle myosin heavy chain isoform SMemb [human, umbilical cord, fetal aorta,
103	1.03	0.533	40739_at	M83670	Hs.89485	762	carbonic anhydrase IV
104	1.03	0.533	39057_at	L04733	Hs.117977	3831	kinesin 2 (60-70kD)
105	1.03	0.532	35625_at	X94630	Hs.3107	976	CD97 antigen

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
106	1.03	0.531	40742_at	M16591	Hs.89555	3055	hemopoietic cell kinase
107	1.03	0.531	38717_at	AL050159	Hs.288771	25840	DKFZP586A0522 protein
108	1.03	0.531	32254_at	AL050223	Hs.194534	6844	vesicle-associated membrane protein 2 (synaptobrevin 2)
109	1.03	0.531	38026_at	U01244	Hs.79732	2192	fibulin 1
110	1.02	0.530	37958_at	AL049257	Hs.8769	83604	hypothetical protein DKFZp761J17121
111	1.02	0.530	37598_at	D79990	Hs.80905	9770	Ras association (RalGDS/AF-6) domain family 2
112	1.02	0.530	39145_at	J02854	Hs.9615	10398	myosin regulatory light chain 2, smooth muscle isoform
113	1.02	0.530	40775_at	AL021786	Hs.17109	9452	integral membrane protein 2A
114	1.02	0.529	35282_r_at	M33680	Hs.54457	975	CD81 antigen (target of antiproliferative antibody 1)
115	1.02	0.529	37023_at	J02923	Hs.76506	3936	lymphocyte cytosolic protein 1 (L-plastin)
116	1.02	0.529	38748_at	U76421	Hs.85302	104	adenosine deaminase, RNA-specific, B1 (homolog of rat RED1)
117	1.01	0.529	41198_at	AF055008	Hs.180577	2896	granulin
118	1	0.528	34194_at	AL049313	Hs.21103		clone DKFZp564B076
119	1	0.528	33158_at	M97252	Hs.89591	3730	Kallmann syndrome 1 sequence
120	0.99	0.528	31525_s_at	J00153			hemoglobin, alpha 2
121	0.99	0.527	32847_at	U48959	Hs.211582	4638	myosin, light polypeptide kinase
122	0.98	0.527	38110_at	AF000652	Hs.8180	6386	syndecan binding protein (syntenin)
123	0.98	0.527	39220_at	T92248	Hs.2240	7356	uteroglobin
124	0.98	0.527	38119_at	X12496	Hs.81994	2995	glycophorin C (Gerbich blood group)
125	0.98	0.527	40936_at	AI651806	Hs.19280	51232	cysteine-rich motor neuron 1
126	0.98	0.527	37194_at	M68891	Hs.334695	2624	GATA-binding protein 2
127	0.97	0.526	41620_at	AB018259	Hs.118140	9732	KIAA0716 gene product

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
128	0.96	0.526	37951_at	AF035119	Hs.8700	10395	deleted in liver cancer 1
129	0.95	0.526	657_at	L11373	Hs.284180	5098	protocadherin gamma subfamily C, 3
130	0.95	0.525	37009_at	AL035079	Hs.76359	847	catalase
131	0.95	0.525	33390_at	AA203487	Hs.314363		CD68
132	0.95	0.525	40434_at	U97519	Hs.16426	5420	podocalyxin-like
133	0.95	0.525	37022_at	U41344			proline arginine-rich end leucine-rich repeat protein
134	0.95	0.525	31792_at	M20560	Hs.1378	306	annexin A3
135	0.94	0.524	38113_at	AB018339	Hs.8182	23345	synaptic nuclei expressed gene 1b
136	0.94	0.524	35152_at	AJ001016	Hs.25691	10268	receptor (calcitonin) activity modifying protein 3
137	0.93	0.524	1879_at	M14949			related RAS viral (r-ras) oncogene homolog
138	0.93	0.524	41734_at	AB020677	Hs.18166	22898	KIAA0870 protein
139	0.92	0.524	36495_at	U21931			fructose-1,6-bisphosphatase 1
140	0.92	0.524	1370_at	M29696	Hs.237868	3575	interleukin 7 receptor
141	0.92	0.523	1598_g_at	L13720	Hs.78501	2621	growth arrest-specific 6
142	0.92	0.523	38363_at	W60864	Hs.9963	7305	TYRO protein tyrosine kinase binding protein
143	0.92	0.523	32035_at	M16942	Hs.318720		MHC class II HLA-DRw53-associated glycoprotein beta-chain
144	0.92	0.523	41209_at	M15856	Hs.180878	4023	lipoprotein lipase
145	0.92	0.523	1612_s_at	X56681	Hs.2780	3727	jun D proto-oncogene
146	0.91	0.523	34091_s_at	Z19554	Hs.297753	7431	vimentin
147	0.91	0.522	479_at	U53446	Hs.81988	1601	disabled (Drosophila) homolog 2 (mitogen-responsive phosphoprotein)
148	0.91	0.522	39615_at	AB028949	Hs.27742	23254	KIAA1026 protein
149	0.9	0.522	692_s_at	J02947	Hs.2420	6649	superoxide dismutase 3, extracellular
150	0.9	0.521	36065_at	AF052389	Hs.4980	9079	LIM domain binding 2
151	0.9	0.521	40570_at	AF032885	Hs.170133	2308	forkhead box O1A (rhabdomyosarcoma)

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
152	0.9	0.521	37148_at	AF025533	Hs.105928	11025	leukocyte immunoglobulin-like receptor, subfamily B (with TM and ITIM domains), member 3
153	0.89	0.521	41288_at	AL036744	Hs.279009	4256	matrix Gla protein
154	0.89	0.521	32811_at	X98507	Hs.286226	4641	myosin IB
155	0.88	0.521	37384_at	D13640	Hs.278441	9647	KIAA0015 gene product
156	0.88	0.520	41325_at	AF006823	Hs.24040	3777	potassium channel, subfamily K, member 3 (TASK)
157	0.88	0.520	40322_at	D12763	Hs.66	9173	interleukin 1 receptor-like 1
158	0.88	0.520	32905_s_at	M30038	Hs.334455	7176	tryptase, alpha
159	0.87	0.520	34873_at	Y16241	Hs.5025	10529	nebulette
160	0.87	0.520	610_at	M15169	Hs.2551	154	adrenergic, beta-2-, receptor, surface
161	0.87	0.520	41644_at	AB018333	Hs.12002	23328	KIAA0790 protein
162	0.87	0.520	36894_at	AL031846			chromobox homolog 7
163	0.87	0.520	33891_at	AL080061	Hs.25035	25932	chloride intracellular channel 4
164	0.87	0.520	40147_at	U18009	Hs.157236	10493	membrane protein of cholinergic synaptic vesicles
165	0.87	0.520	38796_at	X03084	Hs.8986	713	complement component 1, q subcomponent, beta polypeptide
166	0.87	0.520	36856_at	W28743	Hs.7159	80301	hypothetical protein PP1628
167	0.87	0.520	1038_s_at	U19247			interferon gamma receptor 1
168	0.86	0.519	34637_f_at	M12963	Hs.73843	124	alcohol dehydrogenase 1 (class I), alpha polypeptide
169	0.85	0.519	38747_at	M81945			CD34 antigen
170	0.84	0.519	32747_at	X05409	Hs.195432	217	aldehyde dehydrogenase 2, mitochondrial
171	0.84	0.519	32749_s_at	AL050396	Hs.195464	2316	filamin A, alpha (actin-binding protein-280)

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
172	0.84	0.519	38087_s_at	W72186	Hs.81256	6275	S100 calcium-binding protein A4 (calcium protein, calvasculin, metastasin, murine placental homolog)
173	0.84	0.518	38095_i_at	M83664	Hs.814	3115	major histocompatibility complex, class II, DP beta 1
174	0.84	0.518	40203_at	AJ012375	Hs.150580	10209	putative translation initiation factor
175	0.84	0.518	34224_at	AC004770	Hs.21765	3995	flap structure-specific endonuclease 1
176	0.83	0.518	307_at	J03600	Hs.89499	240	arachidonate 5-lipoxygenase
177	0.83	0.518	38968_at	AB005047	Hs.109150	9467	SH3-domain binding protein 5 (BTK-associated)
178	0.83	0.517	39114_at	AB022718	Hs.93675	11067	decidual protein induced by progesterone
179	0.83	0.517	41385_at	AB023204	Hs.103839	23136	differentially expressed in adenocarcinoma of the lung
180	0.83	0.517	39400_at	AB028978	Hs.126084	23102	KIAA1055 protein
181	0.83	0.517	39081_at	AI547258	Hs.118786	4502	metallothionein 2A
182	0.82	0.517	33813_at	AI813532	Hs.256278	7133	tumor necrosis factor receptor superfamily, member 1B
183	0.82	0.517	31775_at	X65018			surfactant, pulmonary-associated protein D
184	0.82	0.517	32855_at	L00352			low density lipoprotein receptor (familial hypercholesterolemia)
185	0.82	0.516	40480_s_at	M14333	Hs.169370	2534	FYN oncogene related to SRC, FGR, YES
186	0.81	0.516	36156_at	U41518	Hs.74602	358	aquaporin 1 (channel-forming integral protein, 28kD)
187	0.81	0.516	41439_at	AJ001381	Hs.121576		incomplete cDNA for a mutated allele of a myosin class I, myh-1c
188	0.81	0.516	774_g_at	D10667			myosin, heavy polypeptide 11, smooth muscle

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
189	0.81	0.516	924_s_at	J03805	Hs.80350	5516	protein phosphatase 2 (formerly 2A), catalytic subunit, beta isoform
190	0.81	0.516	40771_at	Z98946	Hs.170328	4478	moesin
191	0.81	0.515	38833_at	X00457	Hs.914		SB classII histocompatibility antigen alpha-chain
192	0.81	0.515	41143_at	U12022			calmodulin 1 (phosphorylase kinase, delta)
193	0.8	0.515	37176_at	U96078	Hs.75619	3373	hyaluronoglucosaminidase 1
194	0.8	0.515	36447_at	S80990			ficolin (collagen/fibrinogen domain-containing) 1
195	0.8	0.515	1052_s_at	M83667	Hs.76722	1052	CCAAT/enhancer binding protein (C/EBP), delta
196	0.8	0.515	41723_s_at	M32578	Hs.180255	3123	major histocompatibility complex, class II, DR beta 1
197	0.8	0.515	38404_at	M55153	Hs.8265	7052	transglutaminase 2 (C polypeptide, protein-glutamine-gamma-glutamyltransferase)
198	0.8	0.515	34760_at	D14664	Hs.2441	9936	KIAA0022 gene product
199	0.79	0.515	32569_at	L13385	Hs.77318	5048	platelet-activating factor acetylhydrolase, isoform Ib, alpha subunit (45kD)
200	0.79	0.514	505_at	U43077	Hs.160958	11140	CDC37 (cell division cycle 37, S. cerevisiae, homolog)

Table 6: Colorectal Matastasis Markers

[00136] According to the invention, preferred markers are markers 1-30, preferably 1-20, and more preferably 1-10. Highly preferred markers are cytokeratin 20 and villin 1.

Class: Colon

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
1	2.33	0.914	40392_at	U51096	Hs.77399	1045	caudal type homeo box transcription factor 2
2	1.58	0.728	40736_at	X83228	Hs.89436	1015	cadherin 17, LI cadherin (liver-intestine)
3	1.55	0.719	37124_i_at	J04813	Hs.104117	1577	cytochrome P450, subfamily IIIA (niphedipine oxidase), polypeptide 5
4	1.52	0.715	169_at	U51095	Hs.1545	1044	caudal type homeo box transcription factor 1
5	1.45	0.701	40043_at	X71345	Hs.58247	5647	protease, serine, 4 (trypsin 4, brain)
6	1.4	0.698	35644_at	AB014598	Hs.31720	9843	hephaestin
7	1.37	0.688	38586_at	M10050	Hs.5241	2168	fatty acid binding protein 1, liver
8	1.37	0.682	32972_at	Z83819	Hs.132370	27035	NADPH oxidase 1
9	1.34	0.679	39951_at	L20826	Hs.430	5357	plastin 1 (I isoform)
10	1.3	0.677	1229_at	U78556	Hs.166066	10903	cisplatin resistance associated
11	1.3	0.677	988_at	X16354	Hs.50964	634	carcinoembryonic antigen-related cell adhesion molecule 1 (biliary glycoprotein)
12	1.3	0.669	37415_at	AB018258	Hs.109358	23120	ATPase, Class V, type 10B
13	1.25	0.668	41708_at	AB028957	Hs.12896	23314	KIAA1034 protein
14	1.22	0.656	765_s_at	AB006781	Hs.5302	3960	lectin, galactoside-binding, soluble, 4 (galectin 4)
15	1.21	0.654	39697_at	U26726	Hs.1376	3291	hydroxysteroid (11-beta) dehydrogenase 2
16	1.2	0.650	33559_at	U61412			PTK6 protein tyrosine kinase 6
17	1.2	0.649	33904_at	AB000714	Hs.25640	1365	claudin 3
18	1.19	0.649	41266_at	X53586	Hs.227730	3655	integrin, alpha 6
19	1.19	0.648	36170_at	D83198	Hs.7486	23474	protein expressed in thyroid
20	1.18	0.648	37847_at	AB006955	Hs.132945	10083	PDZ-73 protein

BNSDOCID: <WO_____03029273A2_I_>

	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
21	1.16	0.646	34595_at	AF105424	Hs.5394	4640	myosin, heavy polypeptide-like (110kD)
22	1.16	0.644	40694_at	X73502	Hs.84905	54474	cytokeratin 20
23	1.14	0.639	35415_at	X12901	Hs.166068	7429	villin 1
24	1.14	0.638	899_at	L38517	Hs.69351	3549	Indian hedgehog (Drosophila) homolog
25	1.11	0.638	37875_at	U79725	Hs.143131	10223	glycoprotein A33 (transmembrane)
26	1.11	0.635	41678_at	AF025304	Hs.125124	2048	EphB2
27	1.1	0.632	32649_at	X59871	Hs.169294	6932	transcription factor 7 (T-cell specific, HMG-box)
28	1.08	0.629	35114_at	AF084645	Hs.118138	8856	nuclear receptor subfamily 1, group I, member 2
29	1.07	0.629	36832_at	AB015630	Hs.69009	10331	transmembrane protein 3
30	1.07	0.627	41396_at	AB006629	Hs.104717	7461	cytoplasmic linker 2
31	1.07	0.624	35256_at	AL096737	Hs.5167		clone DKFZp434F152
32	1.07	0.620	33436_at	Z46629	Hs.2316	6662	SRY (sex determining region Y)-box 9 (campomelic dysplasia, autosomal sex-reversal)
33	1.05	0.620	33789_at	AF088219	Hs.272493	6359	small inducible cytokine subfamily A (Cys-Cys), member 23
34	1.05	0.619	34450_at	M73489	Hs.1085	2984	guanylate cyclase 2C (heat stable enterotoxin receptor)
35	1.04	0.619	31355_at	U77629	Hs.135639	430	achaete-scute complex (Drosophila) homolog-like 2
36	1.03	0.618	39732_at	X73882	Hs.146388	9053	microtubule-associated protein 7
37	1.03	0.617	40061_at	D83784	Hs.154104	5326	pleiomorphic adenoma gene-like 2

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
38	1.03	0.617	38469_at	M35252	Hs.84072	7103	transmembrane 4 superfamily member 3
39	1.03	0.615	246_at	M25629	Hs.123107	3816	kallikrein 1, renal/pancreas/salivary
40	1.03	0.613	36742_at	U34249	Hs.337461	89870	ring finger protein 9
41	1.02	0.613	36816_s_at	M28668	Hs.663	1080	cystic fibrosis transmembrane conductance regulator, ATP-binding cassette (sub-family C, member 7)
42	1.01	0.612	38495_s_at	U27328	Hs.169238	2525	fucosyltransferase 3 (galactoside 3(4)-L-fucosyltransferase, Lewis blood group included)
43	1.01	0.611	1973_s_at	V00568	Hs.79070	4609	v-myc avian myelocytomatosis viral oncogene homolog
44	1.01	0.611	37857_at	AL080188	Hs.137556	92211	MT-protocadherin
45	1	0.610	40198_at	L06132	Hs.149155	7416	voltage-dependent anion channel 1
46	0.99	0.607	33824_at	X74929	Hs.242463	3856	keratin 8
47	0.99	0.607	38160_at	AF011333	Hs.153563	4065	lymphocyte antigen 75
48	0.99	0.607	34280_at	Y09765	Hs.22785	2564	gamma-aminobutyric acid (GABA) A receptor, epsilon
49	0.98	0.606	31608_g_at	AJ002428	Hs.201553	10065	voltage-dependent anion channel 1 pseudogene
50	0.98	0.606	820_at	U77604	Hs.81874	4258	microsomal glutathione S-transferase 2
51	0.98	0.606	34176_at	AF091087	Hs.206501	57228	hypothetical protein from clone 643
52	0.98	0.605	40647_at	Z32684	Hs.78919	7504	Kell blood group precursor (McLeod phenotype)

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
53	0.98	0.604	36655_at	L27476	Hs.75608	9414	tight junction protein 2 (zona occludens 2)
54	0.97	0.604	37050_r_at	AI130910	Hs.76927	10953	translocase of outer mitochondrial membrane 34
55	0.97	0.604	32324_at	X57346	Hs.279920	7529	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, beta polypeptide
56	0.96	0.604	41715_at	Y11312	Hs.132463	5287	phosphoinositide-3-kinase, class 2, beta polypeptide
57	0.96	0.604	40492_at	AB020633	Hs.169600	23045	KIAA0826 protein
58	0.96	0.603	575_s_at	M93036			tumor-associated calcium signal transducer 1
59	0.95	0.603	1756_f_at	D00003	Hs.329704	1575	cytochrome P450, subfamily IIIA (niphedipine oxidase), polypeptide 3
60	0.95	0.603	37950_at	X74496	Hs.86978	5550	prolyl endopeptidase
61	0.95	0.603	35489_at	M82962	Hs.179704	4224	meprin A, alpha (PABA peptide hydrolase)
62	0.95	0.603	39721_at	U09303	Hs.144700	1947	ephrin-B1
63	0.94	0.602	34803_at	AF022789	Hs.42400	9959	ubiquitin specific protease 12
64	0.94	0.602	32587_at	U07802	Hs.78909	678	butyrate response factor 2 (EGF-response factor 2)
65	0.94	0.602	41359_at	Z98265	Hs.26557	11187	plakophilin 3
66	0.93	0.602	1291_s_at	L03840	Hs.165950	2264	fibroblast growth factor receptor 4
67	0.93	0.602	37253_at	X92493	Hs.78406	8395	phosphatidylinositol -4-phosphate 5-kinase, type I, beta
68	0.92	0.601	38005_at	AJ005866	Hs.90078	11046	nucleotide-sugar transporter similar to C. elegans sqv-7

BNSDOCID: <WO_____03029273A2_I_>

	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
69	0.92	0.601	41448_at	AC004080	Hs.110637	3206	even-skipped homeo box 1 (homolog of Drosophila)
70	0.91	0.600	39748_at	AL050021	Hs.14846		clone DKFZp564D016
71	0.91	0.600	35276_at	AB000712	Hs.5372	1364	claudin 4
72	0.9	0.599	37244_at	AA746355	Hs.77917	7347	ubiquitin carboxyl-terminal esterase L3 (ubiquitin thiolesterase)
73	0.9	0.599	41530_at	D16294	Hs.32500	10449	acetyl-Coenzyme A acyltransferase 2 (mitochondrial 3-oxoacyl-Coenzyme A thiolase)
74	0.9	0.598	36289_f_at	U27333	Hs.32956	2528	fucosyltransferase 6 (alpha (1,3) fucosyltransferase)
75	0.9	0.598	36846_s_at	AA121509	Hs.70830	51690	U6 snRNA-associated Sm-like protein LSm7
76	0.89	0.597	35262_at	AF022229	Hs.5215	3692	integrin beta 4 binding protein
77	0.89	0.597	41816_at	AL049851	Hs.57973	29775	hypothetical protein
78	0.89	0.597	38739_at	AF017257	Hs.85146	2114	v-ets avian erythroblastosis virus E26 oncogene homolog 2
79	0.89	0.596	1936_s_at	HG3523-HT4899			Proto-Oncogene C-Myc, Alt. Splice 3, Orf 114
80	0.89	0.596	31948_at	X79563	Hs.1948	6227	ribosomal protein S21
81	0.88	0.596	36687_at	N50520	Hs.75752	1349	cytochrome c oxidase subunit VIIb
82	0.88	0.595	2042_s_at	M15024	Hs.1334	4602	v-myb avian myeloblastosis viral oncogene homolog
83	0.87	0.595	38375_at	AF112219	Hs.82193	2098	esterase D/formylglutathione hydrolase
84	0.86	0.594	35961_at	AL049390	Hs.22689		clone DKFZp586O1318

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
85	0.86	0.594	1582_at	M29540	Hs.220529	1048	carcinoembryonic antigen-related cell adhesion molecule 5
86	0.86	0.594	37888_at	D87449	Hs.82635	23169	KIAA0260 protein
87	0.86	0.594	266_s_at	L33930	Hs.286124	934	CD24 antigen (small cell lung carcinoma cluster 4 antigen)
88	0.86	0.593	31845_at	U32645	Hs.151139	2000	E74-like factor 4 (ets domain transcription factor)
89	0.86	0.593	37211_at	M93107	Hs.76893	622	3-hydroxybutyrate dehydrogenase (heart, mitochondrial)
90	0.86	0.592	35345_at	X83618	Hs.59889	3158	3-hydroxy-3-methylglutaryl-Coenzyme A synthase 2 (mitochondrial)
91	0.86	0.592	41236_at	U79252	Hs.240062	29787	hypothetical protein
92	0.86	0.592	37698_at	X97335	Hs.78921	8165	A kinase (PRKA) anchor protein 1
93	0.85	0.591	32585_at	AF027299	Hs.7857	2037	erythrocyte membrane protein band 4.1-like 2
94	0.85	0.590	38808_at	D64154	Hs.90107	11047	cell membrane glycoprotein, 110000M(r) (surface antigen)
95	0.85	0.590	37104_at	L40904	Hs.100724	5468	peroxisome proliferative activated receptor, gamma
96	0.85	0.590	1317_at	X70040	Hs.2942	4486	macrophage stimulating 1 receptor (c-met-related tyrosine kinase)
97	0.84	0.590	37413_at	J05257	Hs.109	1800	dipeptidase 1 (renal)
98	0.84	0.589	36345_g_at	U34038	Hs.154299	2150	coagulation factor II (thrombin) receptor-like 1

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
99	0.84	0.589	38036_at	L35035	Hs.79886	22934	ribose 5-phosphate isomerase A (ribose 5-phosphate epimerase)
100	0.84	0.589	39765_at	AB002318	Hs.150443	23079	KIAA0320 protein
101	0.84	0.588	36363_at	U30930	Hs.158540	7368	UDP glycosyltransferase 8 (UDP-galactose ceramide galactosyltransferase)
102	0.84	0.587	1031_at	U09564	Hs.75761	6732	SFRS protein kinase 1
103	0.84	0.587	35913_at	U88047	Hs.198515	1820	dead ringer (Drosophila)-like 1
104	0.83	0.587	39119_s_at	AA631972	Hs.943	9235	natural killer cell transcript 4
105	0.83	0.587	37896_at	AI474125	Hs.82961	7033	trefoil factor 3 (intestinal)
106	0.83	0.587	33892_at	X97675	Hs.25051	5318	plakophilin 2
107	0.83	0.587	1506_at	D11086	Hs.84	3561	interleukin 2 receptor, gamma (severe combined immunodeficiency)
108	0.83	0.587	1237_at	S81914	Hs.76095	8870	immediate early response 3
109	0.82	0.586	35194_at	X53463	Hs.2704	2877	glutathione peroxidase 2 (gastrointestinal)
110	0.82	0.586	36650_at	D13639	Hs.75586	894	cyclin D2
111	0.82	0.586	2075_s_at	L36719	Hs.180533	5606	mitogen-activated protein kinase kinase 3
112	0.82	0.586	40182_s_at	AF055027	Hs.143696	10498	coactivator-associated arginine methyltransferase-1
113	0.82	0.586	786_at	X06745	Hs.267289	5422	polymerase (DNA directed), alpha
114	0.82	0.585	901_g_at	L41349	Hs.283006	5332	phospholipase C, beta 4
115	0.82	0.585	41200_at	Z22555	Hs.180616	949	CD36 antigen (collagen type I receptor, thrombospondin receptor)-like 1

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
116	0.82	0.585	39339_at	AB018335	Hs.119387	9725	KIAA0792 gene product
117	0.81	0.584	41355_at	N95229	Hs.130881	53335	B-cell CLL/lymphoma 11A (zinc finger protein)
118	0.81	0.584	40002_r_at	AI935442	Hs.53542	23230	chorein
119	0.81	0.584	40404_s_at	U18291	Hs.1592	8881	CDC16 (cell division cycle 16, S. cerevisiae, homolog)
120	0.81	0.583	40893_at	AF058953	Hs.182217	8803	succinate-CoA ligase, ADP-forming, beta subunit
121	0.8	0.583	34840_at	AI700633	Hs.288232		cDNA, 3 end
122	0.8	0.583	36123_at	D87292	Hs.248267	7263	thiosulfate sulfurtransferase (rhodanese)
123	0.8	0.583	33248_at	H94842	Hs.17882		EST
124	0.8	0.582	34866_at	AF055029	Hs.4988		clone 24711
125	0.8	0.582	34255_at	AF059202	Hs.288627	8694	diacylglycerol O-acyltransferase (mouse) homolog
126	0.8	0.582	37186_s_at	U11863	Hs.75741	26	amiloride binding protein 1 (amine oxidase (copper-containing))
127	0.8	0.582	41223_at	M22760	Hs.181028	9377	cytochrome c oxidase subunit Va
128	0.79	0.581	34335_at	AI765533	Hs.30942	1948	ephrin-B2
129	0.79	0.581	34712_at	AB023227	Hs.23860	23268	KIAA1010 protein
130	0.79	0.581	1350_at	U02388	Hs.101	8529	cytochrome P450, subfamily IVF, polypeptide 2
131	0.79	0.580	34829_at	U59151	Hs.4747	1736	dyskeratosis congenita 1, dyskerin
132	0.79	0.580	40527_at	AF000571	Hs.156115	3784	potassium voltage-gated channel, KQT-like subfamily, member 1
133	0.79	0.580	37757_at	L23959	Hs.79353	7027	transcription factor Dp-1

BNSDOCID: <WO_____03029273A2_I_>

	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
134	0.79	0.580	37926_at	D14520	Hs.84728	688	Kruppel-like factor 5 (intestinal)
135	0.79	0.580	38048_at	D84110	Hs.80248	11030	RNA-binding protein gene with multiple splicing
136	0.78	0.579	1562_g_at	U27193	Hs.41688	1850	dual specificity phosphatase 8
137	0.78	0.579	36059_at	AB011540	Hs.4930	4038	low density lipoprotein receptor-related protein 4
138	0.78	0.579	36580_at	AL050139	Hs.75277	64795	hypothetical protein FLJ13910
139	0.78	0.579	37263_at	U55206	Hs.78619	8836	gamma-glutamyl hydrolase (conjugase, folylpolygammaglutamyl hydrolase)
140	0.78	0.579	38381_at	U32315	Hs.82240	6809	syntaxin 3A
141	0.78	0.579	37534_at	Y07593	Hs.79187	1525	coxsackie virus and adenovirus receptor
142	0.77	0.578	34998_at	AF059531	Hs.152337	10196	protein arginine N-methyltransferase 3(hnRNP methyltransferase S. cerevisiae)-like 3
143	0.77	0.578	35492_at	AC004523	Hs.180570	66002	hypothetical protein similar to rat CYP4F1
144	0.77	0.578	2089_s_at	H06628	Hs.199067	2065	v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 3
145	0.77	0.578	39362_r_at	AF043906	Hs.121068	7105	transmembrane 4 superfamily member 6
146	0.77	0.578	37690_at	U61263	Hs.78880	10994	ilvB (bacterial acetolactate synthase)-like
147	0.77	0.577	35029_at	Y07828	Hs.91096	11074	ring finger protein
148	0.77	0.577	31849_at	AB011136	Hs.151385	23078	KIAA0564 protein
149	0.77	0.577	40333_at	U43842	Hs.68879	652	bone morphogenetic protein 4

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
150	0.77	0.577	1827_s_at	M13929			c-myc-P64 mRNA, initiating from promoter P0, (HLmyc2.5)
151	0.76	0.577	33103_s_at	U37122	Hs.324470	120	adducin 3 (gamma)
152	0.76	0.576	38247_at	U67058	Hs.168102		Coagulation factor II (thrombin) receptor-like 1
153	0.76	0.576	31854_at	AF035582	Hs.151469	8573	calcium/calmodulin -dependent serine protein kinase (MAGUK family)
154	0.76	0.576	35932_at	AF081507			left-right determination, factor B
155	0.76	0.576	39540_at	AF000561	Hs.104640	51341	HIV-1 inducer of short transcripts binding protein
156	0.76	0.576	41713_at	U09848	Hs.132390	7586	zinc finger protein 36 (KOX 18)
157	0.76	0.576	35444_at	AC004030	Hs.71779		Cosmid F21856
158	0.75	0.576	39219_at	U20240	Hs.2227	1054	CCAAT/enhancer binding protein (C/EBP), gamma
159	0.75	0.575	37672_at	Z72499	Hs.78683	7874	ubiquitin specific protease 7 (herpes virus-associated)
160	0.75	0.575	32502_at	AL041124	Hs.6748	81544	hypothetical protein PP1665
161	0.75	0.574	37423_at	U30246	Hs.110736	6558	solute carrier family 12 (sodium/potassium/ chloride transporters), member 2
162	0.75	0.574	37720_at	M22382	Hs.79037	3329	heat shock 60kD protein 1 (chaperonin)
163	0.75	0.574	1445_at	AF014958	Hs.302043	9034	chemokine (C-C motif) receptor-like 2
164	0.75	0.574	36821_at	AL050367	Hs.66762		clone DKFZp564A026
165	0.75	0.573	37188_at	X92720	Hs.75812	5106	phosphoenolpyruvat e carboxykinase 2 (mitochondrial)

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
166	0.75	0.573	37177_at	Y00636	Hs.75626	965	CD58 antigen, (lymphocyte function-associated antigen 3)
167	0.75	0.573	31669_s_at	AF039307	Hs.249171	3207	homeo box A11
168	0.75	0.573	35673_at	U02082	Hs.334	7984	Rho guanine nucleotide exchange factor (GEF) 5
169	0.75	0.573	283_at	L16842	Hs.119251	7384	ubiquinol-cytochrome c reductase core protein I
170	0.75	0.572	35727_at	AI249721	Hs.39850	54963	hypothetical protein FLJ20517
171	0.74	0.572	40445_at	AF017307	Hs.166096	1999	E74-like factor 3 (ets domain transcription factor, epithelial-specific)
172	0.74	0.572	1943_at	X51688	Hs.85137	890	cyclin A2
173	0.74	0.572	39801_at	AF046889	Hs.153357	8985	procollagen-lysine, 2-oxoglutarate 5-dioxygenase 3
174	0.74	0.572	288_s_at	L25931	Hs.152931	3930	lamin B receptor
175	0.74	0.571	32320_at	Z11502	Hs.181107	312	annexin A13
176	0.74	0.571	37501_at	Y07707	Hs.119018	55922	transcription factor NRF
177	0.73	0.571	476_s_at	U50079	Hs.88556	3065	histone deacetylase 1
178	0.73	0.571	864_at	U07664			homeo box HB9
179	0.73	0.570	34046_at	Z83844	Hs.97858	23616	hypothetical protein dJ37E16.5
180	0.73	0.570	1385_at	M77349	Hs.118787	7045	transforming growth factor, beta-induced, 68kD
181	0.73	0.570	31887_at	J04469	Hs.153998	1159	creatine kinase, mitochondrial 1 (ubiquitous)
182	0.73	0.570	36764_at	AC004125	Hs.7235	10368	calcium channel, voltage-dependent, gamma subunit 3
183	0.73	0.570	35140_at	R59697	Hs.25283	1024	cyclin-dependent kinase 8
184	0.73	0.570	367_at	Z29067	Hs.2236	4752	NIMA (never in mitosis gene a)-related kinase 3

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
185	0.73	0.569	41276_at	W27641	Hs.23964	10284	sin3-associated polypeptide, 18kD
186	0.73	0.569	37562_at	L11370	Hs.79769	5097	protocadherin 1 (cadherin-like 1)
187	0.73	0.569	38630_at	AL080192	Hs.101282		clone DKFZp434B102)
188	0.73	0.569	40123_at	D87435	Hs.155499	8729	golgi-specific brefeldin A resistance factor 1
189	0.73	0.569	32601_s_at	AC004382	Hs.279832	55715	small inducible cytokine subfamily A (Cys-Cys), member 17
190	0.72	0.569	33573_at	AB009426			apolipoprotein B mRNA editing enzyme, catalytic polypeptide 1
191	0.72	0.569	35656_at	AJ010346	Hs.32597	6049	ring finger protein (C3H2C3 type) 6
192	0.72	0.569	39876_at	AL035252	Hs.12330	955	ectonucleoside triphosphate diphosphohydrolase 6 (putative function)
193	0.72	0.569	2064_g_at	L20046	Hs.48576	2073	excision repair cross-complementing rodent repair deficiency, complementation group 5 (xeroderma pigmentosum, complementation group G (Cockayne syndrome))
194	0.72	0.569	40067_at	M82882	Hs.154365	1997	E74-like factor 1 (ets domain transcription factor)
195	0.72	0.568	34339_at	AB009282	Hs.79103	80777	cytochrome b5 outer mitochondrial membrane precursor
196	0.72	0.568	38518_at	Y18004	Hs.171558	10389	sex comb on midleg (Drosophila)-like 2
197	0.71	0.567	37809_at	U41813	Hs.127428	3205	homeo box A9

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
198	0.71	0.567	36613_at	U09585	Hs.315177	7866	interferon-related developmental regulator 2
199	0.71	0.567	31324_at	U82303	Hs.123080		unknown protein mRNA
200	0.71	0.567	308_f_at	J03756	Hs.65149	2689	growth hormone 2

Table 7: C0 Markers

[00137] According to the invention, preferred markers are markers 1-30, preferably 1-20, and more preferably 1-10.

Class: C0

	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
1	0.81	0.681	493_at	U29171	Hs.75852	1453	casein kinase 1, delta
2	0.8	0.620	39431_at	AJ132583	Hs.293007	9520	Aminopeptidase puromycin sensitive
3	0.78	0.599	1953_at	AF024710	Hs.73793	7422	vascular endothelial growth factor
4	0.75	0.584	34678_at	AL096713	Hs.234680	26509	fer-1 (C.elegans)-like 3 (myoferlin)
5	0.73	0.570	32919_at	AC004010	Hs.121520		BAC clone GS099H08
6	0.72	0.545	884_at	M59911	Hs.265829	3675	integrin, alpha 3 (antigen CD49C, alpha 3 subunit of VLA-3 receptor)
7	0.71	0.531	38261_at	AF085692	Hs.90786	8714	ATP-binding cassette, sub-family C (CFTR/MRP), member 3
8	0.7	0.528	33889_s_at	D79985	Hs.2491	9993	DiGeorge syndrome critical region gene 2
9	0.7	0.524	31888_s_at	AF001294	Hs.154036	7262	tumor suppressing subtransferable candidate 3
10	0.69	0.522	38127_at	Z48199	Hs.82109	6382	syndecan 1
11	0.66	0.514	38132_at	M88338	Hs.148101	11135	serum constituent protein
12	0.65	0.511	2017_s_at	M64349	Hs.82932	893	cyclin D1 (PRAD1: parathyroid adenomatosis 1)

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
13	0.64	0.510	36101_s_at	M63978			vascular endothelial growth factor
14	0.64	0.509	33354_at	AA630312	Hs.194477	64750	E3 ubiquitin ligase SMURF2
15	0.64	0.507	32206_at	AB007920	Hs.18586	9876	KIAA0451 gene product
16	0.61	0.499	168_at	U50196	Hs.94382	132	adenosine kinase
17	0.61	0.492	39962_at	U59305	Hs.44708	8476	Ser-Thr protein kinase related to the myotonic dystrophy protein kinase
18	0.6	0.489	33944_at	S60099	Hs.279518	334	amyloid beta (A4) precursor-like protein 2
19	0.6	0.488	32094_at	AB017915	Hs.158304	9469	carbohydrate (chondroitin 6/keratan) sulfotransferase 3
20	0.6	0.486	40504_at	AF001601	Hs.169857	5445	paraoxonase 2
21	0.59	0.485	36117_at	L13616	Hs.740	5747	PTK2 protein tyrosine kinase 2
22	0.58	0.480	34256_at	AB018356	Hs.225939	8869	sialyltransferase 9 (CMP-NeuAc:lactosylceramide alpha-2,3-sialyltransferase; GM3 synthase)
23	0.57	0.477	35212_at	AF064801	Hs.28285	11236	patched related protein translocated in renal cancer
24	0.57	0.476	34796_at	X63679	Hs.4147	23471	translocating chain-associating membrane protein
25	0.56	0.475	40229_at	AJ010071	Hs.153504	10040	target of myb1 (chicken) homolog-like 1
26	0.55	0.473	34793_s_at	M22299	Hs.4114	5358	plastin 3 (T isoform)
27	0.55	0.473	38643_at	W87466	Hs.246885	55041	hypothetical protein FLJ20783
28	0.55	0.472	35350_at	AB011170	Hs.6079	51363	B cell RAG associated protein
29	0.55	0.471	38028_at	AL050152	Hs.301914	55885	clone DKFZp586K1220
30	0.55	0.471	1030_s_at	U07806	Hs.317	7150	topoisomerase (DNA) I

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
31	0.54	0.469	37741_at	M77836	Hs.79217	5831	pyrroline-5-carboxylate reductase 1
32	0.54	0.469	35294_at	M25077	Hs.554	6738	Sjogren syndrome antigen A2 (60kD, ribonucleoprotein autoantigen SS-A/Ro)
33	0.53	0.468	38306_at	AA477576	Hs.94631	10565	brefeldin A-inhibited guanine nucleotide-exchange protein 1
34	0.53	0.467	33128_s_at	W68521	Hs.83393	1474	cystatin E/M
35	0.53	0.463	40471_at	Y09048	Hs.168670	5824	peroxisomal farnesylated protein
36	0.52	0.462	31680_at	M55630			topoisomerase I pseudogene 2
37	0.52	0.460	41140_at	U05875	Hs.177559	3460	interferon gamma receptor 2 (interferon gamma transducer 1)
38	0.52	0.459	33931_at	X71973	Hs.2706	2879	glutathione peroxidase 4 (phospholipid hydroperoxidase)
39	0.52	0.459	393_s_at	X90976	Hs.129914	861	runt-related transcription factor 1 (acute myeloid leukemia 1; aml1 oncogene)
40	0.52	0.459	36036_at	J05500	Hs.47431	6710	spectrin, beta, erythrocytic (includes spherocytosis, clinical type I)
41	0.51	0.459	39411_at	AL080156	Hs.12813	25976	DKFZP434J214 protein
42	0.51	0.459	33454_at	AF016903	Hs.273330	180	agrin
43	0.51	0.458	33121_g_at	AF045229	Hs.82280	6001	regulator of G-protein signalling 10
44	0.5	0.458	40093_at	X83425	Hs.155048	4059	Lutheran blood group (Auberger b antigen included)
45	0.5	0.456	977_s_at	Z35402	Hs.194657	999	cadherin 1, type 1, E-cadherin (epithelial)

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
46	0.5	0.456	33421_s_at	AB016247	Hs.288031	6309	sterol-C5-desaturase (fungal ERG3, delta-5-desaturase)-like
47	0.5	0.455	39712_at	AI541308	Hs.14331	6284	S100 calcium-binding protein A13
48	0.49	0.452	33894_at	AJ010046	Hs.25155	10276	neuroepithelial cell transforming gene 1
49	0.49	0.451	38042_at	X03674	Hs.80206	2539	glucose-6-phosphate dehydrogenase
50	0.49	0.450	32715_at	N90862	Hs.172684	8673	vesicle-associated membrane protein 8 (endobrevin)
51	0.49	0.448	41273_at	AL046940	Hs.250723	79086	hypothetical protein MGC2747
52	0.49	0.448	40303_at	U85658	Hs.61796	7022	transcription factor AP-2 gamma (activating enhancer-binding protein 2 gamma)
53	0.49	0.446	39277_at	U60805	Hs.238648	9180	oncostatin M receptor
54	0.48	0.446	35597_at	AJ000480	Hs.7837	10221	phosphoprotein regulated by mitogenic pathways
55	0.48	0.444	38423_at	L38935	Hs.83086		GT212 mRNA
56	0.48	0.444	291_s_at	J04152	Hs.23582	4070	tumor-associated calcium signal transducer 2
57	0.48	0.444	34885_at	AJ002308	Hs.5097	9144	synaptogyrin 2
58	0.48	0.444	37001_at	M23254	Hs.76288	824	calpain 2, (m/II) large subunit
59	0.48	0.443	40928_at	W26496	Hs.187991	26118	DKFZP564A122 protein
60	0.48	0.443	41078_at	D63484	Hs.98508	23144	KIAA0150 protein
61	0.47	0.443	32034_at	AF041259	Hs.155040	7764	zinc finger protein 217
62	0.47	0.442	37912_at	X80200	Hs.8375	9618	TNF receptor-associated factor 4
63	0.47	0.442	36933_at	D87953	Hs.75789	10397	N-myc downstream regulated
64	0.47	0.442	35442_at	AB007958	Hs.169431	57243	KIAA0489 protein
65	0.47	0.442	33754_at	U43203	Hs.197764	7080	thyroid transcription factor 1

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
66	0.47	0.442	34823_at	X60708	Hs.44926	1803	dipeptidylpeptidase IV (CD26, adenosine deaminase complexing protein 2)
67	0.47	0.441	35276_at	AB000712	Hs.5372	1364	claudin 4
68	0.47	0.441	40088_at	X84373	Hs.155017	8204	nuclear receptor interacting protein 1
69	0.46	0.440	1274_s_at	L22005	Hs.76932	997	cell division cycle 34
70	0.46	0.440	39698_at	U51712	Hs.13775	84525	hypothetical protein SMAP31
71	0.46	0.440	37103_at	AF070610	Hs.100543		clone 24505
72	0.46	0.439	39382_at	AB011089	Hs.12372	23321	KIAA0517 protein
73	0.46	0.439	37360_at	U66711	Hs.77667	4061	lymphocyte antigen 6 complex, locus E
74	0.46	0.439	32640_at	M24283	Hs.168383	3383	intercellular adhesion molecule 1 (CD54), human rhinovirus receptor
75	0.45	0.438	38762_at	AF083255	Hs.8765	11325	RNA helicase-related protein
76	0.45	0.438	39021_at	AB020684	Hs.11217	23333	KIAA0877 protein
77	0.45	0.437	35326_at	AF004876	Hs.5809	10897	putative transmembrane protein; homolog of yeast Golgi membrane protein Yif1p (Yip1p-interacting factor)
78	0.45	0.437	33942_s_at	AF004563	Hs.239356	6812	syntaxin binding protein 1
79	0.45	0.435	32830_g_at	X97544	Hs.20716	10440	translocase of inner mitochondrial membrane 17 (yeast) homolog A
80	0.44	0.435	33448_at	AB000095	Hs.233950	6692	serine protease inhibitor, Kunitz type 1
81	0.44	0.434	36201_at	D13315	Hs.75207	2739	glyoxalase I
82	0.44	0.434	2035_s_at	M55914	Hs.284127	4346	MYC promoter-binding protein 1
83	0.44	0.433	34759_at	U68494	Hs.24385		hbc647 mRNA sequence
84	0.44	0.433	38819_at	U33635	Hs.90572	5754	PTK7 protein tyrosine kinase 7

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Table 8: Other Markers

Class: Other

	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
1	0.46	0.436	608_at	M12529	Hs.169401	348	apolipoprotein E
2	0.45	0.427	1665_s_at	HG544-HT544			Endothelial Cell Growth Factor 1
3	0.45	0.373	35820_at	X62078			GM2 ganglioside activator protein
4	0.45	0.369	33338_at	M97936	Hs.21486	6772	transcription factor ISGF-3
5	0.44	0.362	37219_at	X72755	Hs.77367	4283	monokine induced by gamma interferon
6	0.43	0.362	33956_at	AB018549	Hs.69328	23643	MD-2 protein
7	0.42	0.355	34663_at	M28696	Hs.278443	2213	low-affinity IgG Fc receptor (beta-Fc-gamma-RII)
8	0.42	0.355	36879_at	M63193	Hs.73946	1890	endothelial cell growth factor 1 (platelet-derived)
9	0.41	0.354	36651_at	X15525	Hs.75589	53	acid phosphatase 2, lysosomal
10	0.41	0.353	37542_at	D86961	Hs.79299	10184	lipoma HMGIC fusion partner-like 2
11	0.4	0.351	33143_s_at	U81800	Hs.85838	9123	solute carrier family 16 (monocarboxylic acid transporters), member 3
12	0.4	0.350	36753_at	AF072099	Hs.67846	11006	leukocyte immunoglobulin-like receptor, subfamily B (with TM and ITIM domains), member 4
13	0.39	0.349	34342_s_at	AF052124	Hs.313	6696	secreted phosphoprotein 1 (osteopontin, bone sialoprotein I, early T-lymphocyte activation 1)
14	0.38	0.347	37310_at	X02419	Hs.77274	5328	plasminogen activator, urokinase
15	0.38	0.346	39008_at	M13699	Hs.296634	1356	ceruloplasmin (ferroxidase)
16	0.37	0.344	35714_at	U89606	Hs.38041	8566	pyridoxal (pyridoxine, vitamin B6) kinase

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
17	0.37	0.344	36661_s_at	X06882	Hs.75627	929	CD14 antigen
18	0.36	0.342	38077_at	X52022	Hs.80988	1293	collagen, type VI, alpha 3
19	0.36	0.340	32488_at	X14420	Hs.119571	1281	collagen, type III, alpha 1 (Ehlers-Danlos syndrome type IV, autosomal dominant)
20	0.36	0.340	39945_at	U09278	Hs.418	2191	fibroblast activation protein, alpha
21	0.36	0.339	128_at	X82153	Hs.83942	1513	cathepsin K (pycnodysostosis)
22	0.36	0.336	31859_at	J05070	Hs.151738	4318	matrix metalloproteinase 9 (gelatinase B, 92kD gelatinase, 92kD type IV collagenase)
23	0.36	0.335	32306_g_at	J03464	Hs.179573	1278	collagen, type I, alpha 2
24	0.35	0.334	40297_at	AC005053	Hs.61635	26872	six transmembrane epithelial antigen of the prostate
25	0.35	0.333	771_s_at	D00749			CD7 antigen (p41)
26	0.35	0.331	40496_at	J04080	Hs.169756	716	complement component 1, s subcomponent
27	0.35	0.329	1184_at	D45248	Hs.179774	5721	proteasome (prosome, macropain) activator subunit 2 (PA28 beta)
28	0.34	0.329	1717_s_at	U45878	Hs.127799	330	baculoviral IAP repeat-containing 3
29	0.34	0.329	1039_s_at	U22431	Hs.197540	3091	hypoxia-inducible factor 1, alpha subunit (basic helix-loop-helix transcription factor)
30	0.34	0.328	32193_at	AF030339	Hs.286229	10154	plexin C1
31	0.34	0.328	464_s_at	U72882	Hs.50842	3430	interferon-induced protein 35
32	0.34	0.325	41471_at	W72424	Hs.112405	6280	S100 calcium-binding protein A9 (calgranulin B)
33	0.33	0.325	368_at	Z29083	Hs.82128	10860	5T4 oncofetal trophoblast

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	s2n_obs	Perm 0.1%	non_norm_list	GB/TIGR Identifier	UNIGENE (as of summer 2001)	LL_num	Desc (unigene/locuslink or affy)
34	0.33	0.323	195_s_at	U28014	Hs.74122	837	glycoprotein caspase 4, apoptosis-related cysteine protease
35	0.33	0.323	34386_at	AF072250	Hs.35947	8930	methyl-CpG binding domain protein 4
36	0.33	0.322	38631_at	M92357	Hs.101382	7127	tumor necrosis factor, alpha-induced protein 2
37	0.33	0.321	37220_at	M63835			Fc fragment of IgG, high affinity Ia, receptor for (CD64)
38	0.33	0.321	32700_at	M55543	Hs.171862	2634	guanylate binding protein 2, interferon-inducible
39	0.32	0.320	32434_at	D10522	Hs.75607	4082	myristoylated alanine-rich protein kinase C substrate (MARCKS, 80K-L)
40	0.32	0.320	34666_at	X07834	Hs.318885	6648	superoxide dismutase 2, mitochondrial
41	0.32	0.320	1633_g_at	U77735	Hs.80205	11040	pim-2 oncogene
42	0.32	0.319	39827_at	AA522530	Hs.111244	54541	hypothetical protein
43	0.32	0.319	231_at	M55153	Hs.8265	7052	transglutaminase 2 (C polypeptide, protein-glutamine-gamma-glutamyltransferase)
44	0.32	0.319	35474_s_at	Y15915	Hs.172928	1277	collagen, type I, alpha 1
45	0.32	0.318	40712_at	D26579	Hs.86947	101	a disintegrin and metalloproteinase domain 8
46	0.32	0.317	1042_at	U27185	Hs.82547	5918	retinoic acid receptor responder (tazarotene induced) 1
47	0.32	0.317	37922_at	L02648	Hs.84232	6948	transcobalamin II; macrocytic anemia
48	0.32	0.316	35816_at	U46692	Hs.695	1476	cystatin B (stefin B)
49	0.32	0.315	38111_at	X15998	Hs.81800	1462	chondroitin sulfate proteoglycan 2 (versican)

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Table 9 – Group 1

Rank	s2n v. s2n v. Feature	Genbank_or_tigi	Description
1	0.89 0.57 493_at	U29171	casein kinase 1, delta
2	0.80 0.53 39431_a	AJ132583	puromycin sensitive aminopeptidase
3	0.78 0.52 1953_at	AF024710	vascular endothelial growth factor (VEGF)
4	0.75 0.52 34678_at	AL096713	fer-1 (C. elegans)-like 3 (myoferlin)
5	0.74 0.51 36100_at	AF022375	vascular endothelial growth factor (VEGF)
6	0.73 0.51 32919_at	AC004010	BAC clone GS099H08
7	0.72 0.50 884_at	M59911	integrin, alpha 3 (CD49C antigen)
8	0.71 0.49 38261_at	AF085692	ATP-binding cassette, sub-family C (CFTR/MRP)
9	0.70 0.49 31888_s_at	AF001294	tumor suppressing subtransferable condidate 3
10	0.69 0.48 38127_at	Z48199	syndecan 1
11	0.69 0.46 33889_s_at	D79985	DiGeorge syndrome critical region gene 2
12	0.66 0.46 38132_at	M88338	serum constituent protein
13	0.65 0.45 2017_s_at	M64349	cyclin D1 (PRAD1: parathyroid adenomatosis 1)
14	0.64 0.45 36101_s_at	M63978	vascular endothelial growth factor (VEGF)
15	0.64 0.45 33354_at	AA630312	E3 ubiquitin ligase SMURF2
16	0.64 0.45 32206_at	AB007920	KIAA0450 gene product
17	0.64 0.44 1930_at	U83659	ATP-binding cassette, sub-family C (CFTR/MRP)
18	0.64 0.44 40237_at	AF035444	tumor suppressing subtransferable candidate 3
19	0.61 0.44 168_at	U50196	Adenosine kinase
20	0.61 0.44 39962_at	U59305	ser-thr protein kinase PK428
21	0.60 0.44 33944_at	S60099	Amyloid beta (A4) precursor-like protein 2
22	0.60 0.44 32094_at	AB017915	condoroitin 6-sulfotransferase
23	0.60 0.44 40504_at	AF001601	paraoxoriase 2
24	0.59 0.44 36117_at	L13616	PTK2, focal adhesion kinase
25	0.59 0.44 40229_at	AJ010071	target of myb1-like

Class - CM

Rank	s2n v. s2n v Feature	Genbank or tigi	Description
1	2.29 0.84 40392 at	U51096	caudal type homeo box transcription factor 2
2	1.99 0.64 170_at	U51096	caudal type homeo box transcription factor 2
3	1.60 0.64 40736_at	X83228	cadherini 17, LI cadherin (liver-intestine)
4	1.55 0.63 37124_i_at	J04813	cytochrome P450, subfamily IIIA (niphedipine oxidase)

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Rank	s2n v. s2n v	Feature	Genbank or tigi	Description
5	1.53 0.61	169_at	U51095	caudal type homeo box transcription factor 1
6	1.48 0.60	40043_at	X71345	serine protease, trypsinogen IV
7	1.40 0.59	35644_at	AB014598	Hephaestin
8	1.38 0.59	32972_at	Z83819	NADPH oxidase 1
9	1.38 0.59	38586_at	M10050	fatty acid binding protein 1, liver
10	1.33 0.58	39951_at	L20826	plastin 1 (I isoform)
11	1.30 0.57	988_at	X16354	Carcineombryonic antigen-related cell adhesion molecule 1
12	1.30 0.57	1229_at	U785566	Cisplatin resistance associated
13	1.30 0.57	37415_at	AB018258	ATPase, Class V, type 10B
14	1.27 0.57	41708_at	AB028957	KIAA1034 protein
15	1.22 0.56	765_s_at	AB006781	galectin 4
16	1.22 0.56	40694_at	X73502	cytokeratin 20
17	1.20 0.56	39697_at	U26726	hydroxysteroid (11-beta) dehydrogenase 2
18	1.20 0.56	33904_at	AB000714	claudin 3
19	1.20 0.56	33559_at	U61412	protein tyrosine kinase PTK6
20	1.19 0.56	41266_at	X53586	Integrin, alpha 6
21	1.19 0.55	35415_at	X12901	villin 1
22	1.19 0.55	36170_at	D83198	protein expressed in thyroid
23	1.18 0.55	37847_at	AB006955	PDZ-73 protein
24	1.16 0.55	34595_at	AF105424	myosin IA
25	1.16 0.55	37125_f_at	J04813	cytochrome P450, subfamily IIIA (niphedipine oxidase)

Class – C1

Rank	s2n v: s2n v	Feature	Genbank_or_tigi	Description
1	1.29 0.85	36457_at	U10860	guanine monophosphate synthetase
2	1.25 0.79	40117_at	D84557	Minichromosome maintenance deficient (mis5, 6. Pombe) 6
3	1.22 0.75	37337_at	A1803447	small nuclear ribonucleoprotein polypeptide G
4	1.21 0.73	41547_at	AF047472	BUB3 homolog
5	1.17 0.69	1055_g_at	M87339	replication factor C
6	1.17 0.69	38840_s_at	L10678	profilin 2
7	1.14 0.68	33839_at	AL096719	profilin 2
8	1.12 0.68	38065_at	X62534	high-mobility group protein 2
9	1.11 0.68	709_at	J00314	tubulin, beta polypeptide
10	1.09 0.67	41583_at	AC004770	flap structure-specific endonuclease 1
11	1.07 0.67	34783_s_at	AF047473	BUB3 homolog
12	1.06 0.67	1824_s_at	J05614	proliferating cell nuclear antigen (PCNA)
13	1.05 0.65	40195_a:	X14850	H2A histone family, member X
14	1.05 0.65	39109_a	AB024704	chromosome 20 open reading frame 1
15	1.05 0.65	207_at	M86752	stress-induced-phosphoprotien 1 (Hsp70/Hsp90 organizing protein)
16	1.04 0.65	1884_s_at	M15796	proliferating cell nuclear antigen (PCNA)
17	1.03 0.64	34763_a	AF020043	chondroitin sulfate proteoglycan 6 (bamacan)

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18	1.03	0.64	572_at	M86699	TTK protein kinase
19	1.02	0.64	40619_a	M91670	ubiquitin carrier protein
20	1.00	0.63	151_s_at	V00599	FK506-binding protein 1A (12kD)
21	1.00	0.63	1803_at	X05360	cell division cycle 2, G1 to S and G2 to M
22	0.99	0.63	1515_at	HG4074-HT4344	Rad2
23	0.98	0.63	34791_a	X52882	t-complex 1
24	0.97	0.63	40690_a	X54942	CDC28 protein kinase 2
25	0.96	0.63	37686_s_at	Y09008	uracil-DNA glycosylse

Class – C2

Rank	S2n v. S2n v. Feature			Genebank_or_tigi	Description
1	1.46	0.77	40035_a	AB012917	kallikrein 11
2	1.28	0.65	40544_g_at	L08424	achaete-acute comlex homolog-like 1
3	1.27	0.59	36606_a	X51405	carboxypeptidase E
4	1.21	0.59	31477_a	L08044	trefoil factor 3 (Intestinal)
5	1.19	0.58	36299_a	X02330	calcitonin/calcitonin-related polypeptide
6	1.17	0.57	40649_a	X64810	proprotein convertase subtilisin/kexin type 1
7	1.16	0.57	40543_a	L08424	achaete-acute complex homolog-like 1
8	1.16	0.57	442_at	X15187	tumor rejection antigen (gp96)1
9	1.11	0.56	37897_s_at	AI985964	trefoil factor 3 (Intestinal)
10	1.06	056	36300_a	X15943	calcitonin/calcitonin-related polypeptide
11	1.02	0.56	39332_a	AF035316	tubulin, beta polypeptide
12	0.97	0.55	39756_g_at	Z93930	X-box binding protein 1
13	0.96	0.54	39135_a	AB018310	KIAA0767 protein
14	0.95	0.54	34785_a	AB028948	KIAA1025 protein
15	0.92	0.53	37617_a	U90912	KIAA1128 protein
16	0.87	0.53	39755_a	Z93930	X-box binding protein 1
17	0.85	0.53	37928_a	AA621555	nuclear transcription factor Y, beta
18	0.85	0.53	1788_s_at	U48807	dual specificity phosphatase 4
19	0.84	0.53	35995_a	AF067656	ZW10 Interactor
20	0.84	0.53	37141_a	U39840	hepatocyte nuclear factor 3, alpha
21	0.83	0.53	40201_a	M76180	dopa decarboxylase
22	0.82	0.52	1823_g_at	HG4677-HT5102	Oncogene Ret/Ptc2
23	0.82	0.52	35800_at	D63391	platelet-activating factor acetylhydrolase
24	0.81	0.52	1822_at	HG4677-HT5102	Oncogen Ret/Ptc2
25	0.81	0.52	37426_at	U80736	trinuclectide repeat containing 9

Class C3

Rank	52n v. 52n v Feature			Genebank_or_tigi	Description
1	1.42	0.67	37669_s_at	U16799	Na+/K+ transporting ATPase
2	1.20	0.61	36066_a:	AB020635	KIAA0828 protein
3	1.17	0.60	33699_a:	M18667	pepsinogen C gene
4	1.06	0.58	1081_at	M33764	Ornithine decarboxylase 1

BNSDOCID: <WO_____03029273A2_I_>

Rank	52n v. 52n v Feature	Genebank_or_tigi	Description
5	1.06 0.57 33396_a:	U12472	Glutathione S-transferase pi
6	1.06 0.57 34319_a:	AA131149	S100 calcium-binding protein P
7	1.04 0.56 829_s_a:	U21689	Glutathione S-transferase pl
8	1.02 0.55 37004_a:	J02761	Pulmonary-associated surfactant
9	1.02 0.55 40409_a:	U46689	Aldehyde dehydrogenase 3 family
10	1.02 0.52 32805_a:	U05861	aldo-ketb reductase family 1
11	1.00 0.52 36203_a:	X16277	Ornithine decarboxylase 1
12	0.99 0.52 33383_f-at	A1820718	Retinoic acid receptor
13	0.99 0.51 33052_a:	U95301	Phospholipase A2
14	0.98 0.51 35207_a:	X76180	Sodium channel, nonvoltage-gated 1 alpha
15	0.98 0.51 38526_a:	U02882	CAMP –specific phosphodiesterase
16	0.97 0.51 38066_a:	M81600	NAD(P)H-quinone oxireductase
17	0.93 0.51 1882_g_at	HA4058-HT4328	Fusion activated Oncogene Aml1-Evi-1
18	.093 0.51 37779_at	Y08134	acid sphingomyelinase-like phosphodiesterase
19	0.92 0.50 38773_at	AB003151	carbonyl reductase 1
20	0.90 0.50 700_s_at	HG371-HT26388	Mucin 1, Epithellial
21	0.89 0.50 35938_at	M72393	phospholipase A2, group IVA
22	0.88 0.50 38986_at	Z49835	glucose regulated protein, 58kD
23	0.88 0.50 40685_at	U10868	aldehyde dehydrogenase 3 family, member B1
24	0.87 0.49 41267_at	AB028972	KIAA1049 protein
25	0.86 0.49 34839_at	AB029027	KIAA1104 protein

Class NL

Rank	s2n v. s2n v. Feature	Genbank_or_tigi	Description
1	1.97 0.61 32542_at	AF063002	four and a half LIM domains 1
2	1.92 0.59 1815_g_at	D50683	TGF-beta II receptor
3	1.82 0.58 36119_at	AF070648	clone 24651 mRNA
4	1.75 0.57 35868_at	M91211	advanced glycosylation end product-specific receptor
5	1.71 0.56 39031_at	AA152406	Cytochrome c oxidase
6	1.70 0.56 37398_at	AA100961	CD31 antgen
7	1.70 0.56 40607_at	U97105	Dihydropyrimidinase-like 2
8	1.70 0.56 40841_at	AF049910	Transforming, acidic coiled-coil containing protein 1
9	1.69 0.55 40331_at	AF035819	Macrophage receptor with collagenous structure
10	1.68 0.55 38454_g_at	X15606	Intercellular adhesion molecule 2
11	1.65 0.55 36569_at	X64559	tetranectin (plasminogen-binding protein)
12	1.63 0.55 39066_at	L38486	Microfibrillar-associated protein 4
13	1.60 0.54 40282_s_at	M84526	adipsin/complement factor D
14	1.60 0.54 34320_at	AL050224	polymerase I and transcript release factor

BNSDOCID: <WO_____03029273A2_I_>

Rank	s2n v. s2n v. Feature	Genbank_or_tigi	Description
15	1.60 0.54 37027_at	M80899	AHNAK nucleoprotein (desmoyokin)
16	1.58 0.54 33328_at	W28612	EST
17	1.58 0.54 1814_at	D50683	TGF-beta II receptor
18	1.58 0.54 35985_at	AB023137	A kinase (PRKA) anchor protein 2
19	1.57 0.53 38177_at	AJ001015	RAMP2
20	1.57 0.53 39775_at	X54488	C1-Inhibitor
21	1.57 0.53 770_at	D00632	glutathione peroxidase 3
22	1.54 0.53 39760_at	AL031781	KH domain RNA binding protein
23	1.54 0.53 268_at	L34657	platelet/endothelial cell adhesion molecule-1 (PECAM-1)
24	1.53 0.52 33756_at	U39447	amine oxidase (vascular adhesion protein 1)
25	1.52 0.52 40419_at	X85116	erythrocyte membrane protein band 7.2 (stomatin)

Class – C5

Rank	s2n v. s2n v Feature	Genbank or tigi	Description
1	1.06 0.73 1411_at	D16154	P-450c11
2	1.04 0.70 37021_at	X16832	Cathepsin H
3	1.02 0.70 534_s_at	U20391	folate receptor 1 (adult)
4	0.95 0.69 38394_at	D42047	KIAA0089 protein
5	0.94 0.67 1460_g_at	M68941	Protein tyrosine phosphatase
6	0.92 0.67 33331_at	U17077	BENE protein
7	0.91 0.65 38336_at	AB023230	K1AA1013 protein
8	0.89 0.65 31883_at	AF025794	Methionine synthase reductase (MTRR)
9	0.88 0.65 35016_at	M13560	la-associated invariant gamma-chain
10	0.88 0.65 37512_at	U89281	Oxidative 3 alpha hydroxysteroid dehydrogenase
11	0.87 0.64 1629_s_at	HG3187-HT3366	Tyrosine Phosphatase 1, Non-Receptor
12	0.86 0.64 38459_g_at	L39945	Cytochrome b5 (CYB5) gene
13	0.86 0.64 34139_at	AL049651	Somatostatin receptor 4
14	0.86 0.63 36965_at	U13616	Ankyrin G (ANK-3)
15	0.85 0.63 130_s_at	X82850	Thyroid transcription factor 1
16	0.85 0.63 593_s_at	M34353	v-ros avian UR2 sarcoma virus oncogene homolog 1
17	0.85 0.63 33278_at	AC004381	SA (rat hypertension-associated) homolog
18	0.85 0.63 821_s_at	U78793	folate receptor alpha (hFR)
19	0.82 0.63 40617_at	AC004381	Hypothetical protein FLJ20274
20	0.82 0.63 35792_at	U67963	Lysophospholipase-like
21	0.80 0.63 38785_at	X52228	mucin 1, transmembrane
22	0.80 0.63 33967_at	M31525	major histocompatibility complex, class II
23	0.80 0.63 34198_at	U12128	APO-1/CD95 (Fas)-associated phosphatase
24	0.80 0.62 33584_at	U35146	CDC2-related kinase
25	0.80 0.62 33249_at	M16801	Nuclear receptor subfamily 3, group C, member 2

BNSDOCID: <WO_____03029273A2_I_>

[00138] The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather then limiting on the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes which come within the meaning and range of equivalency of the claims are intended to be embraced therein.

[00139] Each of the patent documents and scientific publications disclosed hereinabove is incorporated by reference herein in its entirety.

BNSDOCID: <WO_____03029273A2_I_>

CLAIMS

1. A method for classifying lung carcinomas on the basis of gene expression, the method comprising the steps of:

a) assaying an expression level for each of a plurality of genes in a plurality of lung carcinoma samples; and,

b) performing a clustering analysis on the expression levels of step a),

thereby identifying classes of lung carcinomas on the basis of gene expression.

2. The method of claim 1, wherein said clustering analysis is selected from the group consisting of hierarchical clustering and probabilistic clustering.

3. A method for diagnosing a type of lung carcinoma, the method comprising the steps of:

a) assaying an expression level for each of a predetermined number of markers of lung carcinoma in a lung carcinoma sample; and,

b) identifying said lung carcinoma as a predetermined type of lung carcinoma if at least one of said expression levels is greater than a reference expression level.

4. The method of claim 3, wherein said predetermined number is between 2 and 50.

5. The method of claim 3, , wherein said predetermined number is greater than 50.

6. The method of claim 4 or 5, wherein said markers of lung carcinoma are markers of at least two different types of lung carcinoma.

7. The method of claim 3, wherein said type of lung carcinoma is selected from the group consisting of metastatic cancers of non-lung origin, small cell lung carcinomas and non-small cell lung carcinomas.

8. The method of claim 7, wherein said non-small cell lung carcinoma is selected from the group consisting of adenocarcinomas, squamous cell carcinomas, and large cell carcinomas.

9. The method of claim 8, wherein said adenocarcinomas are selected from the group consisting of classes C1, C2, C3, and C4.

10. The method of claim 3, wherein said markers are selected from the group consisting of the genes shown in Tables 1-4.

11. The method of claim 10, wherein said markers are selected from the group consisting of kallikrein 11, achaete-scute complex (Drosophila) homolog-like 1, carboxypeptidase E, trefoil

BNSDOCID: <WO_____03029273A2_I_>

factor 3 (intestinal), calcitonin/calcitonin-related polypeptide alpha, proprotein convertase, dual specificity phosphatase 4, and dopa decarboxylase.

12. The method of claim 3, further comprising the step of providing a prognosis for a patient based on the identification of the type of lung carcinoma.

13. The method of claim 3, further comprising the step of recommending a treatment for a patient based on the identification of the type of lung carcinoma.

14. The method of claim 13, wherein said treatment is tailored to the type of lung carcinoma.

15. A method for detecting lung carcinoma in a patient, the method comprising the steps of:

a) assaying an expression level for a predetermined number of markers for lung carcinoma in a patient sample; and,

b) detecting the presence of a lung carcinoma if at least one of said expression levels is greater than a predetermined reference level.

16. The method of claim 15, wherein said predetermined number is between 2 and 50.

17. The method of claim 15, wherein said predetermined number is greater than 50.

18. The method of claim 15 or 16, wherein said markers of lung carcinoma are markers of at least two different types of lung carcinoma.

19. The method of claim 15, wherein said type of lung carcinoma is selected from the group consisting of metastatic cancers of non-lung origin, small cell lung carcinomas and non-small cell lung carcinomas.

20. The method of claim 19, wherein said non-small cell lung carcinoma is selected from the group consisting of adenocarcinomas, squamous cell carcinomas, and large cell carcinomas.

21. The method of claim 20, wherein said adenocarcinomas are selected from the group consisting of classes C1, C2, C3, and C4.

22. The method of claim 15, wherein said gene is selected from the group consisting of the genes shown in Tables 1-4.

23. The method of claim 22, wherein said markers are selected from the group consisting of kallikrein 11, achaete-scute complex (Drosophila) homolog-like 1, carboxypeptidase E, trefoil factor 3 (intestinal), calcitonin/calcitonin-related polypeptide alpha, proprotein convertase, dual specificity phosphatase 4, and dopa decarboxylase.

24. The method of claim 15, further comprising the step of providing a prognosis for a patient based on the identification of the type of lung carcinoma.

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25. The method of claim 15, further comprising the step of recommending a treatment for a patient based on the identification of the type of lung carcinoma.

26. The method of claim 25, wherein said treatment is tailored to the type of lung carcinoma.

27. A diagnostic array comprising:

a) a solid support; and

b) a plurality of diagnostic agents coupled to said solid support, wherein each of said agents is used to assay the expression level of a specific marker of lung carcinoma.

28. The array of claim 27, wherein each of said diagnostic agents is selected from the group consisting of PNA, DNA, and RNA molecules that specifically hybridize to a transcript from a marker of lung carcinoma.

29. The array of claim 27, wherein each of said diagnostic agents is an antibody that specifically binds to a protein expression product of a marker of lung carcinoma.

30. The array of claim 28 or 29, wherein said marker of lung carcinoma is a gene selected from the group consisting of the genes shown in Tables 1-4.

31. The array of claim 30, wherein said lung carcinoma is an adenocarcinoma, and said marker is selected from the group consisting of kallikrein 11, achaete-scute complex (Drosophila) homolog-like 1, carboxypeptidase E, trefoil factor 3 (intestinal), calcitonin/calcitonin-related polypeptide alpha, proprotein convertase, dual specificity phosphatase 4, and dopa decarboxylase.

32. A diagnostic array consisting of:

a) a solid support; and

b) a plurality of diagnostic agents coupled to said solid support, wherein each of said agents is used to assay the expression level of a specific marker of lung carcinoma.

33. The array of claim 27 or 32, wherein said plurality comprises diagnostic agents characteristic of at least two types of lung carcinoma.

34. A system for maintaining lung cancer marker expression levels, the system comprising a memory device comprising a reference expression level for at least one marker of lung carcinoma.

35. The system of claim 34 further comprising a reference expression level for at least one marker of normal lung.

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36. The system of claim 34, wherein each marker is selected from the group consisting of the genes shown in Tables 1-4.

37. The system of claim 35, wherein each marker is selected from the group consisting of kallikrein 11, achaete-scute complex (Drosophila) homolog-like 1, carboxypeptidase E, trefoil factor 3 (intestinal), calcitonin/calcitonin-related polypeptide alpha, proprotein convertase, dual specificity phosphatase 4, and dopa decarboxylase.

38. The system of claim 35, wherein said memory device is selected from the group consisting of tapes, discs, RAM, ROM, and CDROM.

39. A computer disk comprising reference expression levels for a plurality of markers of lung carcinoma.

40. A computer disk comprising a plurality of markers of lung carcinoma.

41. A method for evaluating a drug candidate, the method comprising the steps of:

a) assaying an expression level for each of a predetermined number of lung cancer marker genes in a cell sample;

b) exposing the cell sample to a drug candidate;

c) assaying an expression level for each of the marker genes in the presence of the drug candidate; and

d) identifying a positive drug candidate as one that decreases expression of at least one of said marker genes.

42. A method for monitoring drug treatment of a patient with lung cancer, the method comprising the steps of:

a) administering a drug to a patient with lung cancer; and

b) assaying the expression level of a predetermined number marker genes, wherein the expression level of the marker genes is an indicator of the disease status of the patient.

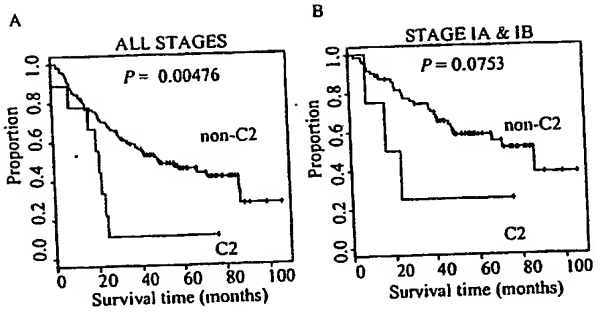
43. A method for classifying a lung carcinoma, the method comprising the steps of:

a) assaying a gene expression profile of a lung carcinoma sample;

b) comparing the gene expression profile of step a) with a reference expression profile characteristic of a known lung carcinoma type; and

c) assigning the lung carcinoma sample to a known lung carcinoma type based on the comparison of step b).

BNSDOCID: <WO_____03029273A2_I_>


A
ALL STAGES
P = 0.00476
non-C2
C2
Proportion
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0 20 40 60 80 100
Survival time (months)
B
STAGE IA & IB
P = 0.0753
non-C2
C2
Proportion
0.0 0.2 0.4 0.6 0.8 1.0
0 20 40 60 80 100
Survival time (months)

Figure 1

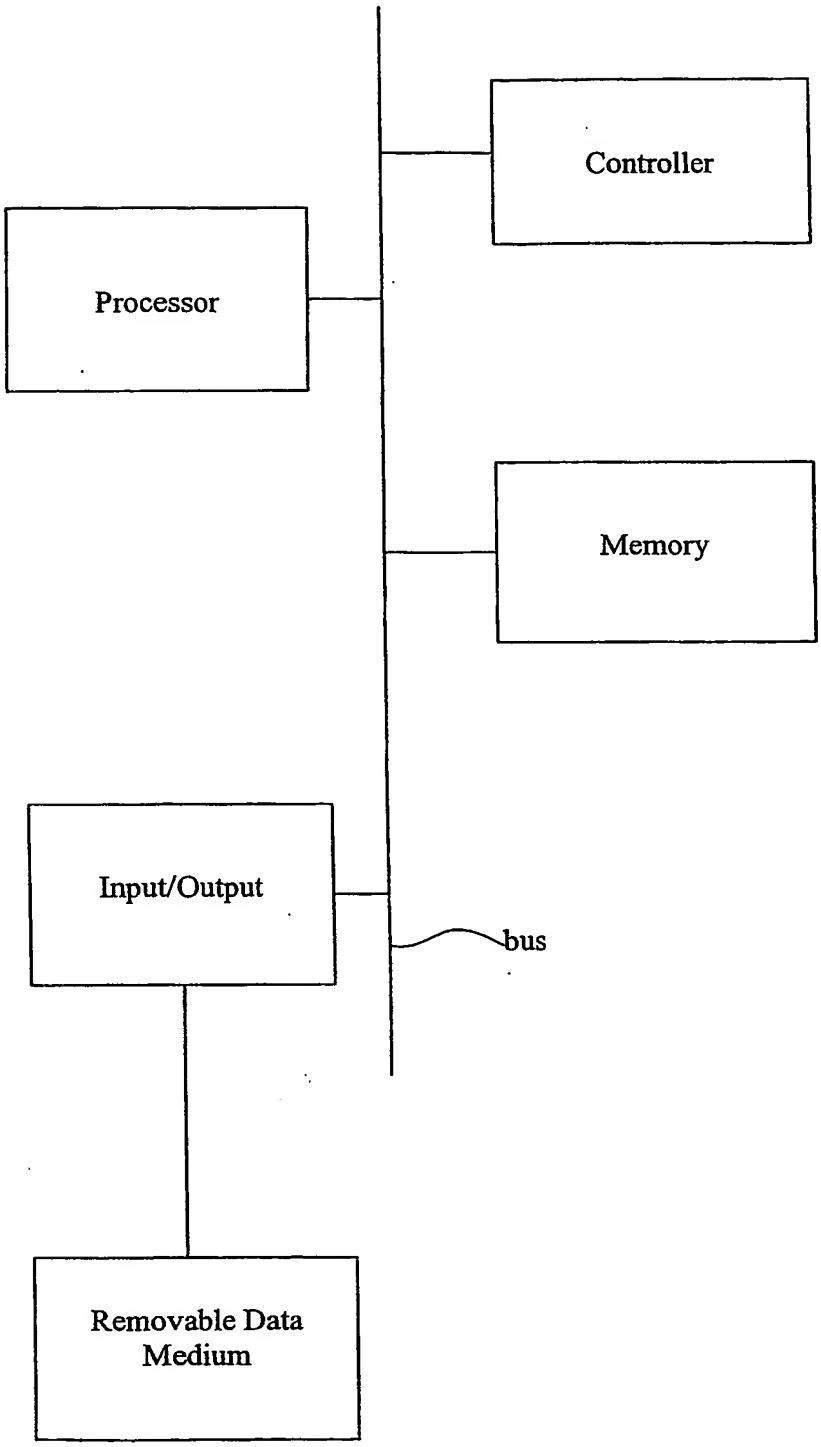
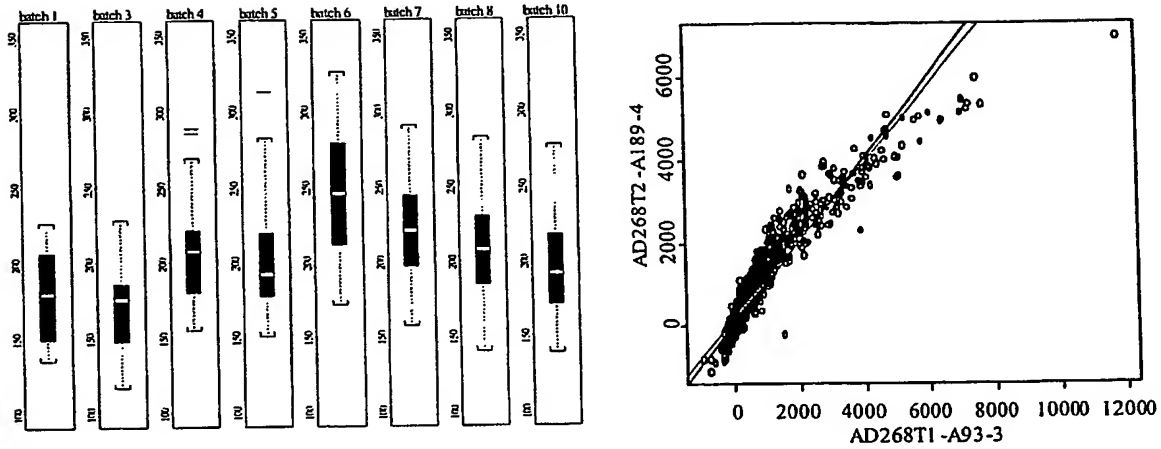

Controller
Processor
Memory
Input/Output
bus
Removable Data Medium

Figure 2

Linear scaling, 2% trimmed mean of "P" genes



Nonlinear rank invariant scaling, 2% trimmed mean of "P" genes

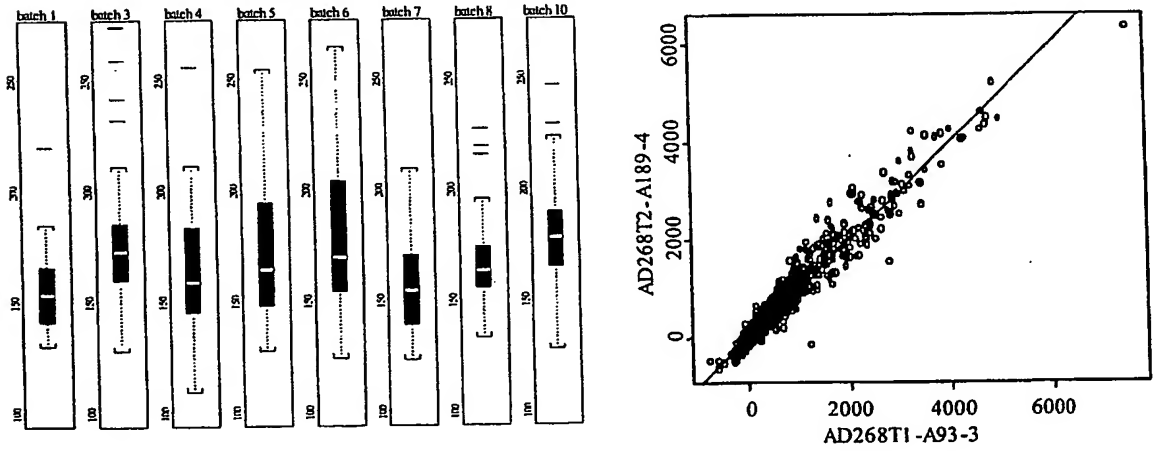


Figure 3

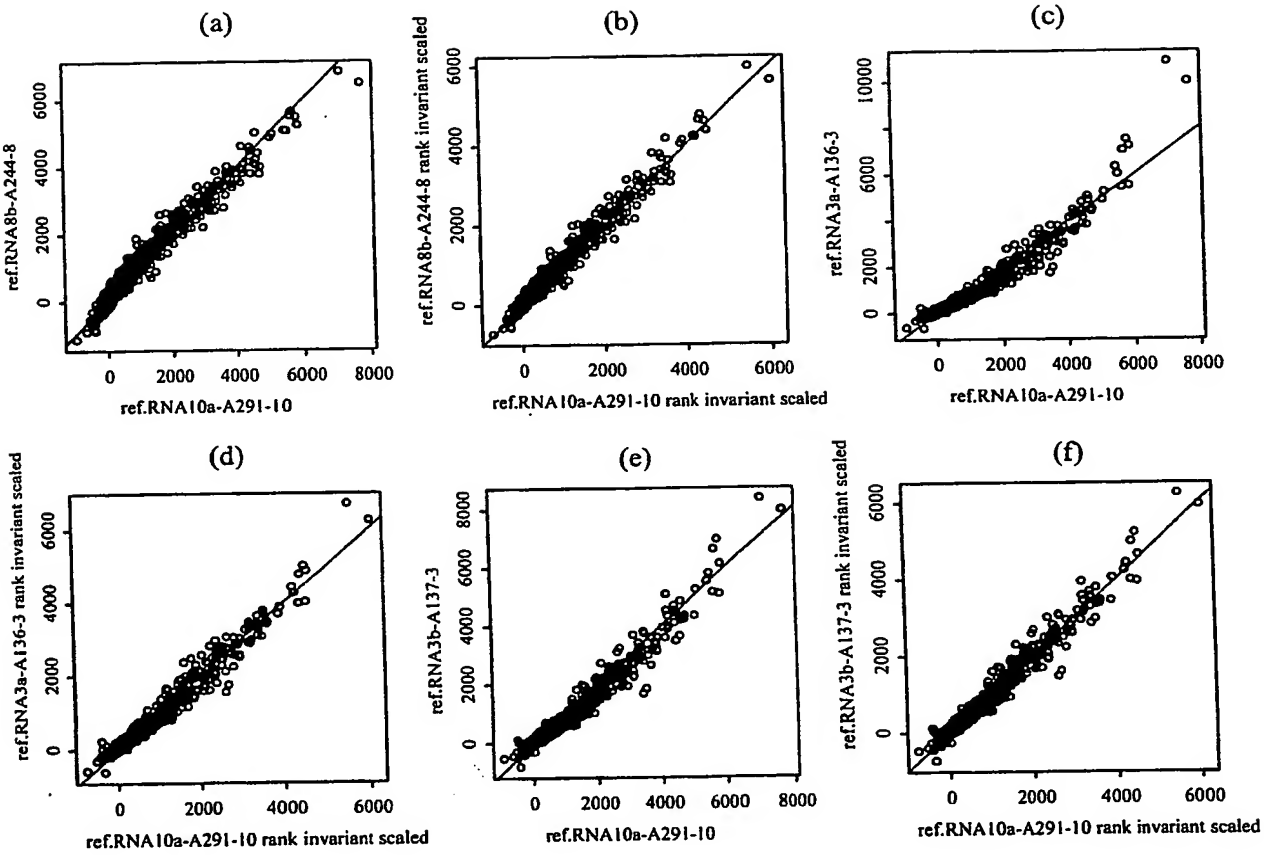

(a)
ref.RNA8b-A244-8
ref.RNA10a-A291-10
(b)
ref.RNA8b-A244-8 rank invariant scaled
ref.RNA10a-A291-10 rank invariant scaled
(c)
ref.RNA3a-A136-3
ref.RNA10a-A291-10
(d)
ref.RNA3a-A136-3 rank invariant scaled
ref.RNA10a-A291-10 rank invariant scaled
(e)
ref.RNA3b-A137-3
ref.RNA10a-A291-10
(f)
ref.RNA3b-A137-3 rank invariant scaled
ref.RNA10a-A291-10 rank invariant scaled

Figure 4

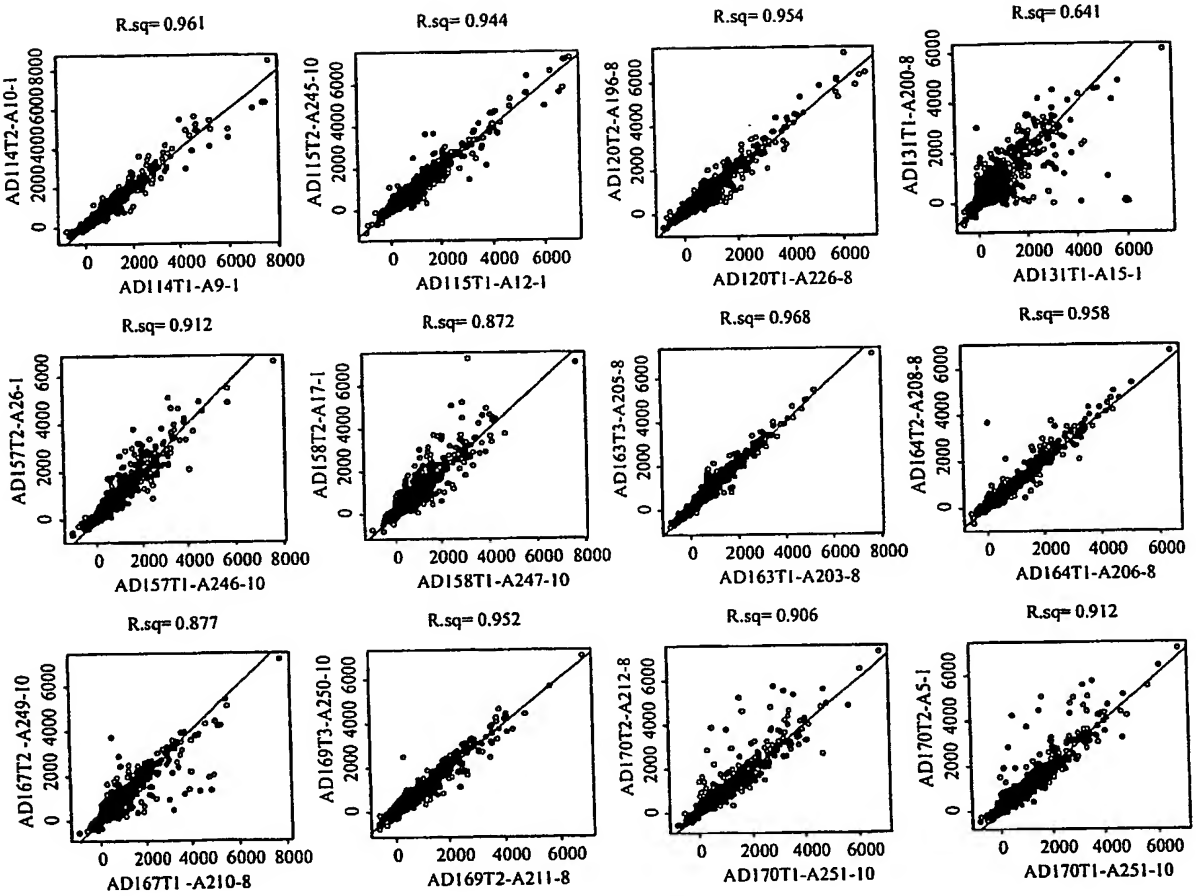

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Figure 5

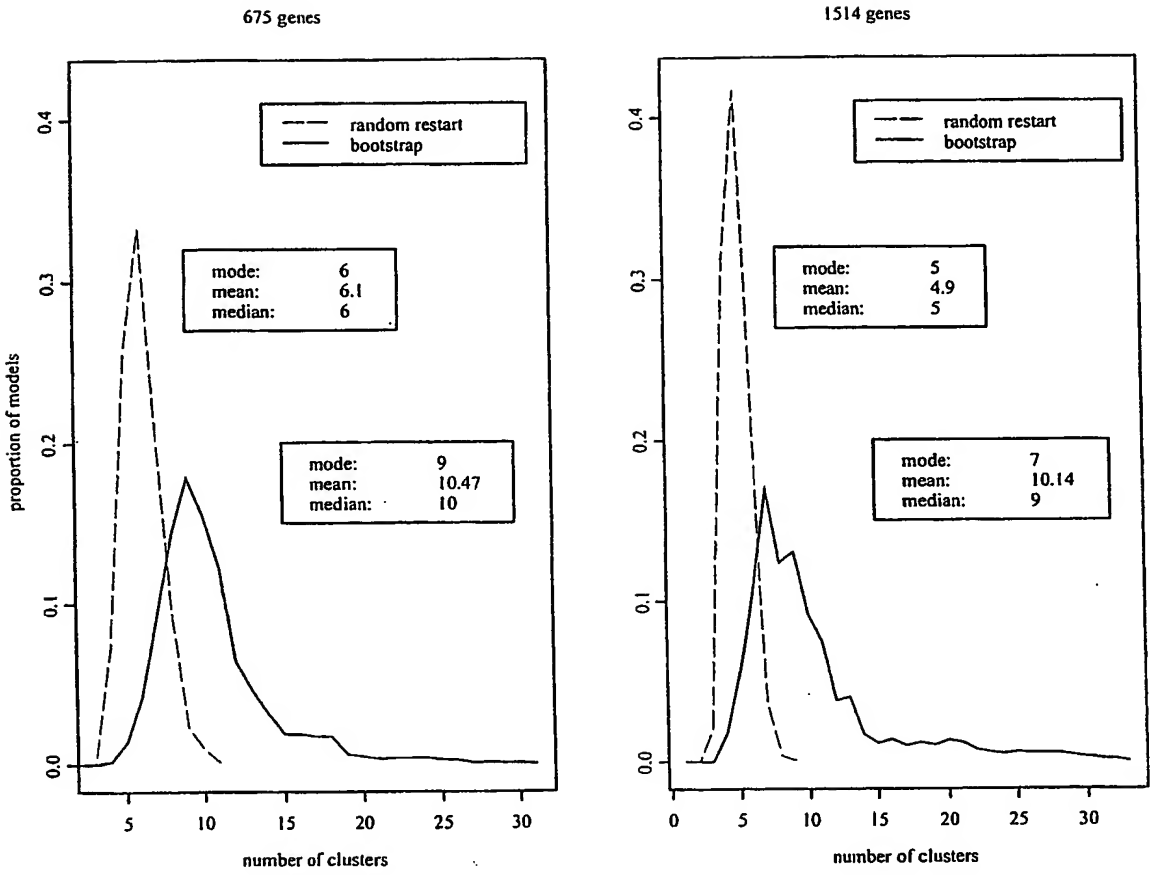
675 genes
random restart
bootstrap
mode: 6
mean: 6.1
median: 6
mode: 9
mean: 10.47
median: 10
proportion of models
number of clusters
1514 genes
random restart
bootstrap
mode: 5
mean: 4.9
median: 5
mode: 7
mean: 10.14
median: 9
number of clusters

Figure 6

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International Bureau

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Published:
— *with international search report*

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20 November 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/029273 A3

(54) Title: CLASSIFICATION OF LUNG CARCINOMAS USING GENE EXPRESSION ANALYSIS

(57) Abstract: The invention provides a molecular taxonomy of lung carcinoma, the leading cause of cancer death in the United States and worldwide. Oligonucleotide micro arrays were used to analyze mRNA expression levels corresponding to 12,600 transcript sequences in 186 lung tumor samples, including 139 adenocarcinomas resected from the lung. Hierarchical and probabilistic clustering of expression data defined distinct subclasses of lung adenocarcinoma. Among these were tumors with high relative expression of neuroendocrine genes and of type II pneumocyte genes, respectively. Retrospective analysis revealed a less favorable outcome for the adenocarcinomas with neuroendocrine gene expression. The diagnostic potential of expression profiling is emphasized by its ability to discriminate primary lung adenocarcinomas from metastases of extrapulmonary origin. These results suggest that integration of expression profile data with clinical parameters could aid in diagnosis of lung cancer patients.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/30797

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C12Q 1/68; C12P 19/34; C07H 21/04
US CL : 435/6, 91.2; 536/24.31, 24.33
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : EAST STN

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Biosis Medline CAplus

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6,040,138 A (LOCKHART et al) 21 March 2000 (21.05.2000), columns 1, 25, lines 13-31, lines 16-26.	1-26 and 43
Y	MONZO, M. et al. A Novel Anti -Apoptosis Gene: Re-expression of Survivin Messenger RNA as a Prognosis Marker in Non-Small-Cell Lung Cancers. Journal of Clinical Oncology. July 1999, Vol. 17, No. 7, pages 2100-2104, especially page 2101.	1-26, 43
Y	HIRST, M. et al. Human GMP Synthetase: Protein purification, cloning, and functional expression of cDNA. J. Biol. Chem. 23 September 1994, Vol. 269, No. 38, pages 23830-23837, especially 23830 and 23837.	9-10, 21-22

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
06 March 2003 (06.03.2003)

Date of mailing of the international search report
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Name and mailing address of the ISA/US
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Form PCT/ISA/210 (second sheet) (July 1998)

BNSDOCID: <WO_____03029273A3_I_>

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/30797

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-26 and 43 drawn to the single Class C1, 1 marker for GMP, U10860

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

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BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

Groups 1-633, Claims 1-26 and 43, drawn to methods of classifying lung tumors, detecting and subsequently diagnosing lung carcinoma in a patient, and recommending treatment, all by assaying the expression level of the same predetermined marker chosen from Tables 1-4(C1-C4 markers). For example, if applicant elects Group 1, then the methods of Claims 1-26 and 43 will be searched as they apply to the expression of a single marker outlined in Tables 1-4, guanine monophosphate synthetase(U10860). Similarly, if applicant elects group 201, claims 1-26 and 43 will be searched as they apply to the marker for kallikein 11(AB012917). If applicant elects group 202, claims 1-26 and 43 will be searched as they apply to the marker, achaete-scute complex (Drosophila_ homolog-like 1(L08424), and so on through C3 and C4 Classes.
Upon election, please specify the marker to be searched, in addition to it respective group.

Groups 634-1266, claims 27, 28, 30-33, drawn to a diagnostic array with a nucleic acid based diagnostic agent that is used to assay the expression level of a specific marker of lung carcinoma. For example, if Group 634 is elected, Claims 27, 28, 30, 31, 32, and 33 will be searched to the extant that the nucleic acid diagnostic agent will bind to the guanine monophosphate synthetase(U10860) marker(The first marker listed in the C1 Class). Similarly, if Group 834 is elected Claims 27, 28, 30-33 will be searched to the extant that the nucleic acid diagnostic agent will bind to the kallikrein 11(AB012917) marker(The first marker listed in the C2 Class).
Upon election, please specify the marker to be searched, in addition to it respective group.

Groups 1267-1899, Claims 27, 29, and 30-33 drawn to a diagnostic array with an antibody that specifically binds to a protein expression product of a marker of lung carcinoma. For example, if Group 1267 is elected, Claims 27, 29, 30, 31, 32, and 33 will be searched to the extant that the antibody diagnostic agent will bind to the protein expression product of the, guanine monophosphate synthetase(U10860) marker(The first marker listed in the C1 Class). Similarly, if Group 1467 is elected Claims 27, 29, 30-33 will be searched to the extant that the antibody diagnostic agent will bind to the kallikrein 11(AB012917) marker(The first marker listed in the C2 Class).
Upon election, please specify the marker to be searched, in addition to it respective group.

Groups 1900-2532, Claims 34-40, drawn to a system and computer disk for maintaining lung cancer marker expression levels, further comprising a reference expression level of a single marker in a normal lung and a single marker selected from Tables 1-4. For example, if applicant elects Group 1900, then claims 34-40 will be searched to the extant that the marker in the system and disk is that of the guanine monophosphate synthetase(U10860) marker.
Upon election, please specify the marker to be searched, in addition to it respective group.

Groups 2533-3164, Claims 41 and 42, drawn to a method for evaluating a drug candidate and for monitoring drug treatment for lung cancer by assaying the expression level of a single marker gene from Tables 1-4. Again, for example, if Group 2533 is elected, the method of claims 41 and 42 will be searched as they apply to the guanine monophosphate synthetase(U10860) marker.

Applicant should note that each set of groups finds its members in each of the markers in the specification listed as Tables 1-4(Classes C1-C4) which total to 633 distinct markers.
The inventions listed as Groups 1-3164 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The method of group 1, in claim 1, includes classifying lung carcinoma on the basis of gene expression by assaying an expression level for each of a plurality of genes in a plurality of lung carcinoma samples in addition to performing a clustering analysis on the expression levels to identify classes of lung carcinoma on the basis of gene expression. Kannan et al.(Oncogene 4/2001) teach the analysis of a human lung cancer cell line and its profile of gene expression regulated by p53 at 32 degrees Celsius using DNA microarrays containing approximately 7000 probes for human genes(abstract). Kannan et al. further taught cluster analysis of these data to identify classes p53 regulated and primary targets in the cell line. As the method of claims 1-26 and 43 does not represent a contribution over the prior art, the claims lack a special technical feature of the other claimed inventions. Thus, there is no special technical feature linking the recited compositions and methods of using said compositions, as would be necessary to fulfill the requirement for unity of invention.

Furthermore, it is also noted that each of the present claims has been presented in improper Markush format, as distinct methods, diagnostic arrays and distinct systems are improperly joined in the claims. Each method, array, and system grouping comprises 633 distinct markers. The markers each consist of a unique nucleotide sequence and differ in their structural and functional properties. Additionally, each combination of markers and method, array and system is distinct from the other in that each combination comprises markers of distinct structure and as a whole each combination is functionally distinct over each other. Each method involving, array

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containing, or system containing combination of markers has a different special technical feature. As the claimed compositions and methods using said markers do not share a special technical feature, the distinct compositions and methods may not properly be presented in the alternative. Accordingly, the claims have been separated into a number of groups corresponding to the number of different inventions encompassed by the claims, and the claims will be searched only as they read upon the elected invention from the methods of Groups 1900-2532, which require, for the system and computer disk used for maintaining lung cancer marker expression levels, different pairs of markers, a single marker from a normal lung and a single marker selected from Tables 1-4.

Further, the claimed methods of groups 1-633 and 2533-3164 have different objectives, require different process steps and require the use of different reagents. The methods of Groups 1-633 require the steps of detecting and subsequently diagnosing lung carcinoma in a patient, and recommending treatment, all by assaying the expression level of the same predetermined marker chosen from Tables 1-4(C1-C4 markers). The methods of Groups 2533-3164 require the steps of evaluating a drug candidate and for monitoring drug treatment for lung cancer by assaying the expression level of a single marker gene. Each of the methods of groups 1-633 and 2533-3164 require the use of different reagents to accommodate the different tasks and different nucleic acids, i.e. a distinct marker for each group. In addition to differences in objectives, effects, and method steps, it is again noted that the claims of the present Groups are not directed to the detection or identification of molecules having the same or common special technical feature, for the reasons discussed above.

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